# Designing Our Descendants

## THE PROMISES AND PERILS OF GENETIC MODIFICATIONS

Edited by Audrey R. Chapman and Mark S. Frankel

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Designing Our Descendants

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# Designing Our Descendants

## The Promises and Perils of Genetic Modifications

Edited by
Audrey R. Chapman
and
Mark S. Frankel

American Association for the Advancement of Science
Washington, D.C.

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# Preface

Rapid breakthroughs in genetic research, spurred by the Human Genome Project, advances in molecular biology, and new reproductive technologies, are raising the prospect that at some point in the future we will have the capacity to design our descendants. There have already been reports of the birth of children with intentionally modified mitochondrial DNA that resulted in unintentional inheritable genetic modification. Within the next generation, some fertility clinics may be inclined to offer services that attempt to control the genetic inheritance of children. The potential magnitude of these interventions makes it very important to improve societal awareness of the technical possibilities, give careful consideration to the implication of their use, and design a process for sustained public discussion before proceeding.

For nearly thirty years, scientists and ethicists have called attention to the need for discussions related to inheritable human genetic interventions. As early as 1972, a few scientists warned that prospective somatic cell gene therapy would carry a risk of inadvertently altering germ cells as well as their targeted somatic cells.[1] In 1982, a presidential commission declared that "especially close scrutiny is appropriate for any procedure that would create inheritable genetic changes."[2] A number of religious bodies and thinkers have urged great caution before proceeding with new technologies that will affect the genetic inheritance of future generations.[3] To date, however, there has been little sustained public consideration of this topic.[4]

In the aftermath of the public furor over the announcement about the successful cloning of the lamb Dolly and the prospect it raised of human cloning, two programs within the American Association for the Advancement of Science (AAAS)—the Program of Dialogue on Science, Ethics, and Religion and the Scientific Freedom, Responsibility and Law Program—decided to undertake a multidisciplinary exploration of issues related to inheritable genetic

modifications with the goal of encouraging public reflection and dialogue. The coeditors of this volume are the director of one of these programs and the former director of the other, and served as the staff directors for the project.

The programs co-organized a two-and-a-half-year project to assess the scientific, ethical, theological, and policy issues related to inheritable genetic modification; formulate recommendations as to what, if any, types of research or applications should be encouraged; and suggest what kinds of safeguards should be instituted. Building on a forum on human germ-line issues co-sponsored by the two programs in September 1997,[5] the project convened a working group of scientists, ethicists, theologians, and policy analysts. Much of the work was conducted in two subgroups, each of which was broadly multidisciplinary in composition. The first subgroup examined the feasibility of various kinds of inheritable genetic interventions, the risks involved, and the appropriate scope and limits of such research and applications on human subjects. The second subgroup considered the social, ethical, and theological implications of such interventions. The working groups met together to formulate findings and craft public policy recommendations. Members of the two working groups are identified in Appendix C.

The first product of the project was an AAAS report, *Human Inheritable Genetic Modifications: Assessing Scientific, Ethical, Religious, and Policy Issues.*[6] This volume is a further development of the analysis, conclusions, and recommendations in that report. Many of the members of the AAAS working group have contributed chapters to this volume.

The volume of twenty chapters is divided into four parts. Part I includes an introduction to the volume and a chapter on definitional issues surrounding IGM that illustrates the importance of defining this area of research in a way that not only fosters sharp analytical treatment, but also offers the clarity necessary for developing public policy.

Part II contains five chapters on the technical dimensions of genetic modification, several by leading researchers in the field of somatic gene therapy. The authors critically examine a wide range of scientific technologies and potentially therapeutic applications related to IGM. The conclusion that can be extrapolated from Part II is that many hurdles remain before IGM would be technically feasible and safe to introduce in humans.

Part III is composed of nine chapters that explore the ethical and religious implications of proceeding with IGM. Issues related to safety, justice, enhancement beyond what is necessary to sustain or restore good health, embry-

onic research, reproductive rights, parent-child relationships, and obligations to our descendants are examined from both secular and theological perspectives. The chapters note that religious and ethical evaluation of IGM will depend on the nature of the technology, its impact on human nature, and the level of safety and efficacy offered, and that IGM to treat disease or disability will make it difficult to avoid use of such interventions for enhancement purposes even when this use is considered ethically unacceptable.

The final set of chapters is devoted to policy issues. The four chapters in Part IV offer a regulatory framework for governing IGM, examine the relationship of IGM to reproductive rights, assess the potential effects of commercialization of IGM research and application, and present recommendations for the type of oversight that should be applied to IGM. The authors of Part IV draw attention to the need for a public oversight system, with clear channels for public input, that should apply to IGM research and applications in both the private and public sectors. The system would also need to address the influence of market forces in shaping the future of IGM, so that public priorities and sensibilities are adequately considered.

We would like to thank members of the working group for the time and effort they devoted to the project (see Appendix C). We are deeply indebted to them for their commitment to the project and their many contributions to the initial report and to this volume. We are especially grateful to Gladys White, who helped keep us abreast of the fast-moving international developments in policy related to human genetic modification.

We also want to thank the Greenwall Foundation for its financial support, which enabled us to conduct the study in a deliberative fashion. It, too, saw the benefit in producing this analysis and generating public dialogue on the issues before the science overtakes society's ability to anticipate the possibilities that lie ahead so that we may make informed and reasoned choices about the future.

Several current and former AAAS staff also contributed to the conduct of the study, the preparation of the initial report, and the production of this volume. We thank Jason Borenstein, Aimee Curtright, Aaron Goldenberg, Monica Hlavac, Margot Iverson, Sharon Leu, Alexander Liroff, Michael MacDonald, Jim Miller, Bhavani Pathak, and Sheryl Wallin. Special thanks to Rachel Gray, who before leaving AAAS coordinated preparation of the manuscript, and Erin LaFarge, who ably helped produce the final manuscript.

NOTES

1. Theodore Friedmann and Richard Robin, "Genetic Therapy for Human Genetic Disease?" *Science* 175 (1972): 952.

2. President's Commission for the Study of Ethical Problems in Medicine and Behavioral Research, *Splicing Life: The Social and Ethical Issues of Genetic Engineering with Human Beings* (Washington, D.C.: U.S. Government Printing Office, November 1982), 3.

3. For a discussion of the religious perspectives, see Audrey R. Chapman, *Unprecedented Choices: Religious Ethics at the Frontiers of Genetic Science* (Minneapolis: Fortress Press, 1999), 8–75.

4. There have been a few efforts to stimulate debate. In March 1998 a symposium entitled "Engineering the Human Germline" was held at UCLA. A publication was issued based on the symposium presentations. See Gregory Stock and John Campbell, eds., *Engineering the Human Germline: An Exploration of the Science and Ethics of Altering the Genes We Pass On to Our Children* (Oxford and New York: Oxford University Press, 2000). See also David B. Resnik, Holly B. Steinkraus, and Pamela J. Langer, *Human Germline Gene Therapy: Scientific, Moral and Political Issues* (Austin: R. G. Landes Company, 1999). More recently, two books have sparked renewed interest in these issues. See Francis Fukuyama, *Our Posthuman Future: Consequences of the Biotechnology Revolution* (New York: Farrar, Strauss, Giroux, 2002), and Gregory Stock, *Redesigning Humans: Our Inevitable Genetic Future* (Boston: Houghton Mifflin, 2002).

5. See www.aaas.org/spp/sfrl/projects/glforum.htm.

6. Mark S. Frankel and Audrey R. Chapman, *Human Inheritable Genetic Modifications: Assessing Scientific, Ethical, Religious, and Policy Issues* (Washington, D.C.: American Association for the Advancement of Science, 2000). The report is available online at www.aaas.org/spp/dspp/sfrl/projects/germline/report.pdf.

CHAPTER ONE

# Framing the Issues

Audrey R. Chapman, Ph.D., and Mark S. Frankel, Ph.D.

Typically, our society proceeds in a "reactionary mode," scrambling to match our values and policy to scientific developments. But doing so has serious limitations. The furor over the possibility of applying somatic cell nuclear transfer technology to clone human beings underscores how difficult it is to undertake a serious examination of the ethical, religious, and societal implications of new technologies after scientific breakthroughs have already been made. Thus, when confronted with a potential scientific advance that raises profound issues related to the possibilities of modifying our genetic futures, it is important to plan ahead, to decide whether and how to proceed with its development, and to give direction to this technology through rigorous analysis and public dialogue. This volume explores the feasibility and implications of proceeding with one such potential innovation, inheritable genetic modifications (IGM), which would confer the ability to design our genetic futures.

Rapid breakthroughs in genetic research spurred by the Human Genome Project, advances in molecular biology, and new reproductive technologies have advanced our understanding of how we might approach genetic interventions as possible remedies for diseases caused by genetic disorders, partic-

ularly for those caused by abnormalities in single genes. Limitations of current medical therapies to treat diseases with a genetic component have led to efforts to develop techniques for treating diseases at the molecular level, by altering a person's cells. To date, most of the research and clinical resources related to gene therapy have been invested in developing techniques for targeting nonreproductive body cells. Somatic gene therapies are intended to treat or eliminate disease only in the individuals receiving treatment. After many years of frustration in attempting to produce techniques for efficient gene transfer of somatic cells, in 2000 clinical scientists published evidence of credible successes in improving the health of patients with two diseases—hemophilia B and X-linked immunodeficiency—through gene transfer, perhaps signaling that years of research are about to bear fruit.[1]

Recent advances in animal research are raising the possibility that we will also eventually have the technical capacity to modify genes that are transmitted to future generations.[2] This volume uses the terminology of IGM to refer to any biomedical intervention that can be expected to modify the genome that a person can transfer to his or her offspring. Earlier literature identified these interventions as "germ-line therapy." One form of IGM would be to alter the germ or reproductive cells that develop into the egg or sperm of a developing organism and transmit its heritable characteristics. Another form of IGM would be to modify the embryo itself. Still other technologies under development, such as the insertion of artificial chromosomes, could also be used to introduce inheritable genetic changes.

In theory, the ability to undertake inheritable genetic modifications could have several advantages over somatic cell gene therapy. IGM offers the possibility of preventing the inheritance of some genetically based diseases within families rather than repeating somatic therapy generation after generation. Because these interventions could influence the earliest stage of human development, the technology also offers the potential for preventing irreversible damage attributable to defective genes before it occurs. Some scientists and ethicists argue that germ-line intervention is medically necessary to prevent certain classes of disorders because there are situations where screening and selection procedures will not be applicable, such as when both parents have the same mutation.[3] Over a long period of time, germ-line gene modification could be used to decrease the incidence of certain inherited diseases in the human gene pool currently causing great suffering.[4]

IGM, however, also raises profound ethical, theological, and policy issues

that need to be thoroughly explored, discussed, and evaluated before further work in this area proceeds. Efforts to modify genes that are transmitted to future generations have the potential to bring about not only a medical but also a social revolution, for they offer us the potential power to mold our children in a variety of novel ways through genetic enhancement. These techniques could confer extraordinary control over biological properties and personality traits that we currently consider essential to our humanness. Even with the technical ability to proceed, we would still need to determine whether these procedures offer a socially and ethically acceptable alternative to other technologies under development to treat genetic diseases. Do we have the wisdom, ethical commitment, and public policies necessary to apply these technologies in a manner that is equitable, just, and respectful of human dignity?

The potential magnitude of these interventions makes it very important to improve societal awareness of the technical possibilities, give careful consideration to the implications of their use, and design a process for sustained public discussion before proceeding. Informed public discussion will require an understanding of the scientific possibilities and risks, as well as the pressing moral concerns this technology raises. This volume is intended as a resource for these purposes.

## Defining Inheritable Genetic Modifications

As used in this volume, inheritable genetic modifications refer to the technologies, techniques, and interventions that are capable of modifying the set of genes that a subject has available to transmit to his or her offspring. IGM includes all interventions made early enough in embryonic or fetal development to have global effects on the gametes' precursor tissues, as well as the sperm and ova themselves. IGM encompasses inheritable modifications regardless of whether the intervention alters nuclear or extranuclear genomes, whether the intervention relies on molecular genetic or other technical strategies, and even whether the modification is a side effect or the central purpose of the intervention.

The kinds of interventions that fall within the scope of the definition of IGM are those that raise the following core issues:

- They are interventions that hold out the prospect of increasing our control over the specific hereditary traits of the next generation and beyond if they succeed.

- They are interventions that make inheritable changes in the genes of surviving offspring, rather than interventions that simply select among offspring on the basis of their naturally inherited genes.
- They are interventions associated with scientific research (i.e., biomedical interventions) rather than social practices.
- They pose the risk of creating iatrogenic and other genetic harms.

## Therapeutic Need

Clear therapeutic need should be the primary criterion for proceeding with IGM, given the investment of resources that would be required to develop effective techniques for germ-line intervention, concerns about safety, and its ethical implications. Yet the study by the American Association for the Advancement of Science (AAAS) identified few instances where IGM would be needed (see Appendix B). There are currently several alternative approaches available to help parents avoid passing on defective genes to offspring. These include genetic screening and counseling, prenatal diagnosis and abortion, preimplantation diagnosis and embryo selection, gamete donation, and adoption. In the future, in utero somatic gene therapy, gene therapy on ill patients, and gene-based pharmaceutical products are likely to offer effective means for correcting many defects. The use of IGM should be weighed for effectiveness, safety, efficiency, and social acceptance against these other means, but it is likely that modifying the germ line will carry with it greater uncertainty regarding outcomes. Moreover, at least initially, IGM will still require prenatal diagnosis with the prospect of selective abortion to prevent the birth of seriously impaired children.

## Efficacy of Different Approaches to IGM

The development of effective gene delivery techniques at the somatic cell level raises the inevitable question of the technical potential and the desirability of genetic modification to affect subsequent generations for either disease prevention or enhancement purposes. For such applications to become feasible would require solutions to a number of technical problems and questions, including the identification of the target cell, the nature and efficiency of the gene delivery methods, and determination of both the short-term safety and long-term disease prevention or enhancement effects as well as the long-range developmental implications of the intervention.

In principle, genes and other foreign genetic elements might be introduced into the germ line of an organism by genetic modification of the gametes themselves, by genetic modification of the fertilized egg, or by gene transfer into the cells of an early embryo in a way that allows gene transfer into the developing gametes. There are several serious technical impediments, however, to safe and effective transfer of foreign genetic material into the human germ line through all of these approaches. One major obstacle is the limited capacity of most transfer methods, which concentrate on replacement of the coding function of a gene unaccompanied by its full complement of regulatory genetic elements to ensure appropriate levels, timing, or distribution of gene expression. The development of new transfer techniques, such as artificial chromosomes, may partially overcome this obstacle, but may generate other problems associated with the presence of excessive amounts of some sequences and the uncertain effects of creating too many chromosome segments compared to the normal genotype.

A further problem is that all current methods are susceptible to uncertainty and error. In biomedicine, as well as in all other forms of scientific research, one must be aware of technical problems and unexpected adverse results in initial studies in order to design appropriate modifications in subsequent experiments. Unfortunately, even in the best hands, current methods are highly inefficient and produce offspring ("founder" animals) that express the foreign genetic material to variable extents in various tissues. Transgene methodology, for example, is exceedingly inefficient, and produces animals possessing the desired traits with an efficiency, at best, of only several percent. The imperfect efficiency of gene transfer that is tolerable in animal studies (which, in unsuccessful experiments, leads to damaged offspring that are subsequently eliminated) would not be acceptable for humans. Current methods do not allow safe and controlled application of these techniques in humans.

## Safety Issues

The AAAS study concluded that it is not now possible to undertake IGM safely and responsibly. Current methods for somatic gene transfer are inefficient and unreliable because they involve addition of DNA to cells rather than correcting or replacing a mutated gene with a normal one. They are therefore inappropriate for human germ-line intervention because they cannot be shown to be safe and effective.

For IGM technologies to meet safety standards, there must be evidence that

the procedures used do not cause unacceptable short-term or long-term consequences for either the treated individual or succeeding generations of offspring. This means that an altered embryo must be able to transit all human developments without a mishap due to the induced intervention. And for those techniques that add foreign material, there must be multigenerational data showing that the modification or improvement of a specific genetically determined trait is stable and effective and does not interfere with the functioning of other genes.

At present, the hazards of IGM are largely unknown and unpredictable. We do not have sufficient biological knowledge and understanding of the human genome to predict the long-term risks from genetically engineering human cells. Manipulating the germ line might generate harmful interactions between inserted or modified genes and other genes in the recipient genome that would have untoward and unanticipated side effects in children. An inadvertently introduced error might in some circumstances become a permanent part of a child's genetic legacy and might affect generations to come. In addition, the elimination of certain disease-linked genes might also remove beneficial effects of having those genes.

Thus, a central requirement for IGM is the development of new technologies that replace deleterious genes by homologous recombination or some other method of gene replacement or correction rather than by gene addition. Gene replacement would minimize the potential for iatrogenic harms and increase the probability of appropriate gene expression across generations of offspring. As a society, we must begin to consider how much evidence of safety and efficacy will be required before permitting either human clinical trials or nonmedical applications.

## Inadvertent Germ-Line Modifications

As somatic gene transfer trials proceed, it is likely that some of the new technologies and approaches may increase the likelihood of secondary germ-line modifications. In utero gene transfer, which has the potential benefit of correcting genetic deficiencies before they produce serious adverse consequences, raises the possibility of inadvertent gene transfer to the germ line. It is also possible that gene correction techniques currently under development may produce secondary germ-line changes.

The possibility of genetic problems occurring as a result of the unintended

germ-line side effects of somatic cell transfer seems at least as great or greater than those that might arise from intentional IGM. Presumably, if researchers were conducting intentional IGM they would be using methods designed to cause the least possible genetic disruption in germ cells. Further, if they were using in vitro embryos, they would attempt to monitor the effects of the genetic manipulation before they implanted an embryo. With intentional IGM, there would be at least some safeguards for minimizing the possibility that a person would be born with iatrogenic genetic damage. The same cannot be said of an inadvertent germ-line modification.

There have already been reports of the birth of children with intentionally modified mitochondrial DNA that resulted in unintentional IGM.[5] Micromanipulation techniques now in use make it possible to compensate for mitochondrial genetic diseases, through either inserting segments of healthy mitochondria or placing the nucleus in a substitute egg (in vitro ovum nuclear transplantation). Some thirty children have been born, fifteen of them as a result of experimental treatment at one U.S. fertility center. Genetic fingerprint tests on some of the babies confirm that they have inadvertently inherited the mitochondrial genes from the donor cytoplasm and will likely produce offspring who will also inherit those genes. Moreover, although the scientists involved claimed a perfect record of healthy births, in fact two of the seventeen fetuses created by the technique at one center had Turner syndrome, a disorder in which an entire chromosome is missing.[6] This kind of private-sector experimentation is unregulated in the United States, but it would be illegal in many countries, including the United Kingdom.

The AAAS study concluded that any somatic genetic transfer applications where there is a reasonably foreseeable possibility of IGM should not proceed at this time. To avoid iatrogenic genetic damage occurring as a result of the unintended germ-line side effects of somatic cell therapy, attention should given to the accompanying side effects of somatic cell therapies already in use or planned. There is also a need for further scientific analysis to assess short- and long-term risks and for public discussion to determine the extent to which there is support for going forward with secondary germ-line changes.

## Religious Perspectives on IGM

Among the world's religious traditions, there is a widely shared presumption in favor of healing. Most faiths endorse medicine in some form as a highly

valued human action. This support often includes the explicit recognition that medicine sometimes treats disease by altering nature in some respect, for example, by interfering with the natural course of a pathogen. Yet, the religious traditions represented in the AAAS study—mainline Protestantism, Catholicism, and Judaism—also share a deep uneasiness regarding actions that might alter human nature or affect human relationships. Such a cautionary approach has marked the responses of religious commentators to nearly every medical advance, and IGM is no exception.

The official positions of most religious communities that have a relevant policy are better characterized as expressing caution rather than categorical rejection of IGM. In many of these policy statements the distinction between the acceptability of somatic cell therapy and the problematic nature of germ-line therapies appears to be made primarily on the grounds of safety rather than intrinsic theological or ethical objection to germ line per se. Many of the documents advocate a temporary moratorium rather than a permanent ban so as to assure safety and provide ample time for ethical reflection to guide scientists and society.[7]

It seems likely that future religious evaluations of IGM will depend on the nature of the technology, its impact on human nature, the level of safety and efficacy, and whether IGM is used for therapeutic or enhancement purposes. The working group identified a series of potential religious concerns with respect to IGM.

### *The Status of the Human Embryo*

Religious traditions vary quite considerably in their views on the status of the human embryo and on the question of whether the embryo is to be regarded as a fully human person from the moment of conception. The fabrication of microscopic embryos entirely outside the womb from extracted gametes, separate from conjugal relationships, introduces unique quandaries unimagined in the canonical texts that govern religiolegal responses in many religious traditions. In the Jewish and Muslim traditions, for example, embryos created in vitro are not even to be considered human. According to these traditions, all embryos, both those created as a result of sexual relationships and those brought into existence through in vitro fertilization (IVF) techniques, are not "ensouled" for the first forty days of conception. Many liberal Christian communities share a developmental view of the human embryo: it is accorded respect and regarded with dignity, but only gradually as the pregnancy pro-

gresses is it considered to achieve the full standing of a human person.[8] In contrast, it is the official position of several major churches and the personal belief of many Christians, as well as adherents of some other traditions, that the human embryo is to be regarded as a human person from conception. This belief implies that the embryo is never to be treated as an object of experiment or research and then be discarded. This concern bears on some, but not all, strategies and techniques that may be used in the development and clinical application of IGM. Such modifications would, for example, be permissible in the Roman Catholic tradition as long as the procedure was clearly therapeutic; did not directly or indirectly destroy or injure the human intellect or will, or otherwise impair their respective functions; and did not involve in vitro fertilization, experimentation on embryos, their destruction in the course of developing the therapy, or the externalization of the embryos during the course of the therapy.[9]

### *Respect for Human Finitude*

Many religions understand humans as limited not only by their ability to understand and comprehend fully but also by the human creaturely condition, driven by needs, temptations, passion, and the fear of death. Religious thinkers tend to share the suspicion that human beings exaggerate their knowledge of and their ability to control nature through technology. As with many other technologies, our ability to foresee the full consequences of going forward with IGM will be partial at best. Hence, there is concern among religious thinkers that our enthusiasm for this technology and its benefits will tend to downplay the limits of our ability to know the effects of our acts and to proceed responsibly.

### *Social Justice*

Many religious traditions have a commitment to social and economic justice and are concerned about the existing unequal access to health care. For people of faith, this inequality violates the belief that the benefits of creation, including those that come in part from human effort, are to be widely shared. This makes many within the religious community particularly sensitive to the issue of equity in access to IGM. There is concern that this technology will enable us to enhance offspring in socially desirable and competitive ways, thereby further privileging the wealthy and powerful by securing the position of their offspring against competition.[10]

### *The Relationship between Parents and Children*

Religious thinkers have worried that too great a readiness to attempt to control the genetic inheritance of our offspring will undermine the value and meaning of the parent-child relationship. Simply put, the intrusion of technology, even if very well intended, could reduce the child to an artifact, a product of technological design, at least in the mind of the child or of his or her parents. Parents would become designers, whose will to have a certain kind of child is etched into the genetic code of their offspring. This is not to glorify the fragile imperfections of nature but to ask a critical question: should we use our technology to alter the relationship so that parents and children become designers and products?

## Ethical Analysis: Intrinsic Considerations

Additional ethical considerations must be taken into account before attempting IGM. The first is whether there are fundamental reasons that such interventions are, in principle, morally impermissible. The second is the social and moral impact these technologies will have on the human community. The AAAS study concluded that if concerns about the safety and reliability of such modifications and their likely deleterious social and justice impact can be addressed, there would seem to be no reason to regard such interventions as morally prohibited in principle. The study analyzed three areas:

1. The Value of Genes.

Some analysts maintain that human genes have a special significance and value because they are biologically essential to our existence as human beings. Others argue that our genes distinguish us from one another as individuals and are at the core of our humanness. While acknowledging that human genes have special significance and value, the AAAS study did not find that the status of genes precludes undertaking IGM.

2. The Impact on the Human Gene Pool.

It has been argued that future generations have a right to inherit an unmodified human gene pool because the gene pool represents a resource to which all people have equal claim as the "common heritage" of our species.[11] Strictly speaking, however, while individual humans have germ-line cells and

germ cell lineages, the human species does not have a "germ line" in the genealogical sense. The human gene pool is a heuristic abstraction, not a natural object, and lacks a material referent in nature. Therefore, while it is important to ensure that future generations have fair access to the benefits of human genetic research, it is conceptually mistaken to interpret the human gene pool as an "endowment" accumulated by the wise investments of natural selection over which we now have stewardship.[12] The evolutionary process that controls the allelic content of the human gene pool is an unmanaged and unmanageable one. The human gene pool is not a stable given, but has been in flux over the course of human history. It is doubtful that IGM would have a serious impact on the gene pool.

3. Lack of Consent by Future Generations.

The AAAS study acknowledged an intergenerational responsibility to guard the interests of future persons, but it took issue with those who claim that this obligation precludes IGM. If we do have responsibilities to our descendants, our obligations undoubtedly encompass efforts to make life better for our children and subsequent descendants. This could include eliminating deleterious genes and thereby improving the health of future generations.

## Ethical Analysis: Contextual Considerations and Societal Impact

Like all technologies, IGM will not be undertaken in the abstract. If we go forward with human applications, these genetic alterations will be conducted through some series of procedures, on particular subjects, for specific purposes, and in concrete social, economic, and cultural contexts. All of these contextual factors will contribute to its impact on society. Among the series of problems related to contextual considerations, the AAAS study identified several issues related to equity and justice of particular concern. Many, but not all, members of the study's working group drew the conclusion that these contextual factors, singly and jointly, indicate that we are not currently at a point where we should allow the development and use of IGM.

### *Inequities in Access to Genetic Therapies*

Unless there are major changes in the health care system in this country, there will likely be a lack of equity in access to IGM. This reflects a number of

factors: the absence of universal health insurance, patterns of inequalities in access to health care in this country, a projected scarcity in the availability of genetic services relative to demand, and the role of market forces in the development of such genetic interventions. Many members of the AAAS working group held the view that as long as we cannot or do not provide basic health care to all members of our society we should not invest in the development of expensive new technologies like IGM. Others also argued that it is pointless to talk about any kind of just distribution of genetic technologies unless and until all persons have access to adequate nutrition, potable water, sanitation, and basic vaccinations. However, other members countered that the world is full of inequalities in health care, but we do not restrict research and use of promising medical technologies.

*Reinforce or Increase Existing Discrimination*

The AAAS study was concerned that as long as Americans still discriminate unfairly on the basis of physical appearance, ancestry, or abilities, the introduction of IGM would pose some risk of exacerbating social prejudices. This is particularly a problem in a country, like our own, which has a long and disturbing history of drawing sharp distinctions among citizens on the basis of race and ethnicity and where many persons harbor beliefs in biological determinism. IGM may increase prejudice against persons with disabilities. This is yet another reason that the development and introduction of IGM techniques should engender concern, scrutiny, and caution, especially since the culture of prejudice is less susceptible to remedy by direct public policy initiatives.

*Challenges to Equality*

IGM would not create new problems of inequity, but it could significantly magnify inequalities already rooted in American culture. IGM would have a cumulative impact: the advantages and enhancements of one generation would be passed on to their progeny. Unequal access to IGM technologies would mean that those persons who can already provide the best "environments" for their children would also be able to purchase the best "natures." Thus, those who had preferential access to life's material goods would be able to purchase genetic improvements for their children and their children's descendants, and thereby become doubly advantaged.

### *Commercialization and Commodification*

Some ethicists and religious thinkers fear that human germ-line manipulation would accelerate tendencies to commodify children and evaluate them according to standards of quality control. The AAAS study found merit in these concerns about commodification. Obviously, IGM will not constitute the source of the attitudes that make science and medicine just one more form of concentrated social power or turn parenting into an exercise of power over offspring for the sake of the satisfaction of parental desires. But it might well exacerbate such attitudes by providing parents with a powerful tool, which, when combined with the natural parental desire to enhance the quality of life of their children, will fuel further research and development of IGM that will require society to confront its uneasiness over commodification.

## Ethically Appropriate Applications of IGM: Therapy versus Enhancement

Like somatic cell interventions, IGM offers the possibility of genetic enhancements, that is, genetic alterations intended to improve what are already "normal" genes. Modifying a complex normal trait will require far more sophisticated knowledge than we currently have about how genetic factors contribute to their development. It will also necessitate developing the technical ability to manipulate several different genes in concert with one another.

One of the reasons why a distinction is made between therapeutic and enhancement germ-line intervention is the fear that the ability to discard unwanted traits and improve wanted characteristics will lead to a form of eugenics. Another theme is that enhancement applications of IGM, especially if this technology is heavily promoted by commercial developments, would encourage affluent parents to attempt to "improve" their future children's genomes so as to endow them with various advantages. Some ethicists express a concern that this dynamic may promote something analogous to a kind of "soft eugenics."[13] Other ethicists have raised the concern that enhancement technologies might lead to the imposition of harmful or skewed conceptions of normality and concomitantly of what constitutes improvement of human traits. Some scientists and ethicists have seen dangers in the effort to define a normal hu-

man genome precisely because it also implies that deviations from the normal sequence would be considered abnormal or undesirable. Others have pointed out the tendency of individuals and societies to seek to impose their own standards and cultural particularities on the world.[14] IGM used for enhancement purposes would inevitably reflect and embody the values held by those sponsoring and having access to the technology, who could then shape the genetic inheritance of future generations. In addition, the literature on enhancement poses the prospect that it will become increasingly difficult to differentiate between prevention and enhancement in genetic medical interventions.[15]

The AAAS study concluded that, with the safety and justice qualifications noted above, the use of IGM to prevent and treat clear-cut diseases in future generations is ethically justifiable and does not constitute a form of eugenics. While acknowledging that there will be difficult borderline cases, the AAAS study concluded that it would be possible to distinguish between IGM applications for therapy and those for enhancement. There were far stronger reservations about undertaking IGM for any enhancement purposes. Most members of the study's working group could only support using IGM for cases that are clearly therapeutic. And many members would add the further qualification that IGM should be pursued only when other treatment options are unavailable.

The dilemma is that IGM techniques developed for therapeutic purposes are likely to be suitable for enhancement applications as well. Thus, going forward with IGM to treat disease or disability will make it difficult to avoid use of such interventions for enhancement purposes even when this use is considered to be ethically unacceptable.

## Reproductive Rights

It has been argued that parents have the right to reproduce and to choose whatever means available, consistent with the technology that exists and avoidance of harm to others, to attempt to ensure a normal pregnancy and healthy baby.[16] Reproductive autonomy is understood as the individual's right to freedom from interference or constraint in the exercise of his or her reproductive capacity, including the right to make choices about conception, contraception, and termination of pregnancy. Advances in genetics and reproductive medicine promise to extend this range of choice. If safe and effective IGM is developed, it would enable parents not only to select the genes of their children, but also to influence the inheritance of their children's progeny.

Is the right to reproduce a global right that includes the right to apply IGM and other forms of "quality control" technologies to select and control the genetic makeup of future offspring? The AAAS study concluded that individuals and couples are not entitled to proceed unimpeded to use these technologies to control the genes of future children in almost any way that they choose. While many legal commentators agree that decisions about whether to have children are deeply significant and should be given considerable scope, it is questionable as to whether the right to reproduce extends to the use of inheritable genetic modifications.

We do not believe that parental authority over children would insulate parental decisions about the use of IGM from state control. In law, as in morality, the comprehensive liberty that parents enjoy in the care and rearing of their children is intended to provide the family with the means to nurture children into adulthood. When parents fall significantly below social standards of adequacy in the fulfillment of their responsibilities toward their children, their parental authority can be legally terminated.

The power afforded by genetics to select the characteristics of our descendants raises important ethical and social issues that are legitimate subjects of public regulation. By extension, government has the authority and responsibility to develop reasonable regulations covering the use of IGM in order to protect the interests of children as well as core values of the community.

This volume addresses the issues outlined above in greater depth. The chapters were enriched by the discussions within the AAAS working group and in most, but not all cases, reflect the concerns and recommendations outlined in the AAAS report. Nevertheless, the essays included in this volume represent the views of the individual authors. We hope this volume will be a contribution to stimulating and informing a dialogue.

ACKNOWLEDGMENTS

This chapter is based on a study conducted by the American Association for the Advancement of Science. See Mark S. Frankel and Audrey R. Chapman, *Human Inheritable Genetic Modifications: Assessing the Scientific, Ethical, Religious and Policy Issues* (Washington, D.C.: American Association for the Advance-

ment of Science, 2000), or www.aaas.org/spp/sfrl/projects/germline/report.pdf. The study's findings and recommendations can be found in Appendix B.

NOTES

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CHAPTER TWO

# Germ-Line Dancing

## Definitional Considerations for Policy Makers

Eric Juengst, Ph.D., and Erik Parens, Ph.D.

Just as "good ethics requires good facts," good policy requires good definitions. That is why the larger parts of so many public laws are devoted to the definition of their key terms: it is in those definitions that the policies find their true mission, their real scope, and their actual power. Because of that, of course, it is also in the definitions that many of the hard choices about a policy must be made. In this chapter, we examine the definitional choices that will confront those charged with making one particular kind of policy: policy governing biomedicine's emerging ability to create inheritable genetic modifications (IGM) in human beings. By policy we mean any official position on the matter, be it institutional, professional, or governmental. For convenience, we will call all those charged with addressing these matters IGM policy makers, whether they do so for a single laboratory, a professional society, or a nation. Their definitional choices are shared, and, we hope to show, the clarification of their choices is far from simple ground clearing. The process of getting clear on just what these policy makers are making policy about, in fact, also suggests some contours of the policy itself.

## The Definitional Problem

The definitional distinction between "germ-line" and "somatic cell" gene therapy has been useful—even crucial—to the early regulation of human gene transfer research. It has allowed policy makers to point out that most of the public's serious qualms about human gene transfer research lay with the introduction of *inheritable* genetic modifications, and thus would only be raised by attempts to transfer genes into human germ-line cells.[1] To allow the nascent field of gene transfer research to proceed without having to resolve the vexing moral problems that inheritable genetic changes were perceived to raise, it was enough simply to postpone or proscribe all attempts to transfer genes into human germ-line cells and focus our regulatory attention on assessing the safety and efficacy of human somatic cell gene transfer protocols.[2] But what techniques and technologies should this distinction hold apart? What should it mean to "transfer genes into the germ line"?

For the past hundred years, the IGM policy makers' definitional task seemed relatively simple. In 1885, the embryologist August Weismann distinguished between what he called *somatische* cells and those possessing what he called *Keimplasma:* the "germ plasm" that allows a sperm and ova to transmit hereditary traits from parents to their offspring.[3] Embraced by American embryologists, the distinction between the tissue lineages in a growing embryo that differentiate into its "germ (plasm) cells" and those that differentiate into its other "somatic" cells has long outlived Weismann's *Keimplasma* theory of inheritance. Of course, its heyday as a provocative scientific distinction passed with the death of the germ plasm theory, especially after we realized that the structures that do carry out the hereditary function—the genes—are actually alive and well in all types of nucleated human cells. With the continuities between generations explained as the expression of *information* encoded in multiple, independently assorting genes (later to be understood as recombining DNA molecules), the "immortal germ plasm" was no longer necessary as a racial "hereditary fluid," except to the eugenicists who embraced it as their poster child.[4] Nevertheless, Weismann's terminology has remained embedded in developmental histology, where "germinal" language continues to be used as a convention to identify the cell lineages whose progeny will eventually undergo meiosis to produce gametes. Moreover, since its centennial birthday, Weismann's somatic/germinal distinction has developed an important second ca-

reer in science policy, as the cornerstone for our thinking about the limits of human gene transfer research.

Fortunately, in its science policy role, the somatic cell/germ cell distinction still does not have to bear much theoretical weight. Although its antiquated language can be confusing, in the context of human gene transfer research it is used simply to signal the fact that only genetic changes introduced into the cell lineages that produce the gametes—the "germ line"—can be transmitted to the next generation, while changes confined to "somatic" cell lines cannot. "Germ-line" interventions thus include changes made early enough in embryonic development to have global effects, like zygote transformation, and interventions later in life that affect the gametes' precursor tissues as well as the sperm and ova themselves.[5]

It is out of this context that today's IGM policy makers inherit the framework for their task. The time has come, apparently, when it is no longer possible to avoid addressing the concerns raised by our ability to create inheritable genetic changes in human beings. Until fairly recently it has been assumed that to craft policies governing the creation of inheritable genetic changes would be to craft policies governing the transfer of single genes to germ cells. The fact that this assumption is no longer well founded is where the new definitional problem starts for IGM policy makers.

In fact, part of the new pressure to consider the "germ-line question" is that it is increasingly likely that biomedicine will be able to create inheritable genetic changes in human beings *without* performing traditional gene transfer interventions on germ-line cells. For example, somatic cell nuclear transfer techniques seem to open the possibility of making any somatic cell capable of passing its genome on to the next generation, including genetically modified somatic cells.[6] Cell fusion techniques and the development of stable "artificial chromosomes" could help us engineer human embryos without the need for any traditional gene transfer interventions at all.[7] For that matter, attempts to avoid mitochondrial diseases by transplanting mitochondria-rich cytoplasm from one egg into another have already led to inheritable genetic changes in human beings, by permanently importing new mitochondrial DNA.[8] Does it matter that, in these cases, the inheritability of the new mitochondrial genome is only an unintended by-product of the attempt to prevent the embryo's eventual somatic cell deficiencies? If not, how should we classify scenarios for in utero somatic cell gene transfer experiments that pose similar risks of acciden-

tally transducing germ-line cells? It may well be that the moral challenge that provoked us to dust off Weismann's somatic cell/germ cell distinction in the first place—the prospect of creating inheritable changes in our children—will actually appear at one of these scientific side doors long before it arrives at the front door of "germ-line gene transfer," where we've been waiting for it.[9]

What all this means for IGM policy makers is that, as new biomedical techniques emerge that give us different ways of changing our children's genomes, it is getting less clear whether the concept of "germ-line interventions" still captures the science relevant to our moral concern about inducing inheritable genetic changes in human beings. If policies are to be made to address the issues raised by that concept, how should we define the domain of those policies today? IGM policy makers will face three definitional options: (1) to define their domain narrowly, in terms of the gene transfer techniques that have occasioned the science policy revival of Weismann's distinction, and accept that many related biomedical techniques raising the same moral concerns will not be subject to the policies they develop; (2) to define the domain broadly, extending the category of "germ-line interventions" to any practice that influences the genetic composition of the next generation, and accept the challenge of crafting the much more sweeping policies that this would require; or (3) to define their domain differently, in terms of the core moral concerns that Weismann's distinction was intended to flag for science policy, rather than in terms of the specific biomedical techniques that raise those concerns today. The challenge of this last option is to define those *core concerns* clearly enough to be useful as jurisdictional criteria for their policy, regardless of the scientific door at which a given intervention appears.

We think that in the end only the third option makes sense. Clearly, the somatic cell/germ cell distinction has not lost all of its relevance to IGM policy making. Gene transfer interventions into germ-line cells still provide the paradigm class of interventions for thinking about the moral concerns that IGM policies should attempt to address. But, as we argue below, the category of "germ-line interventions" alone will not suffice to do all the work IGM policy makers once hoped it would, in either its narrow or broad interpretations. Fortunately, demonstrating this view can also serve to help meet the third option's primary challenge, since in the deficiencies of the first two options lie useful hints about the core moral criteria required for the fuller development of the third.

## Steps in the Definitional Dance

To understand our position, it helps to proceed through the paces of a deliberation about the definitional choices we have listed above. It takes ten steps, not all of which move in the same direction, to complete the pattern.

### *1. Retaining the Narrow Definitional Domain*

The main arguments for adopting the first definitional option for IGM policy making are historical continuity and administrative convenience. To date, the discussion of our concerns about making inheritable genetic changes in human beings has largely been limited to recombinant DNA–based gene transfer techniques and their application to germ-line cells. A scientific community devoted to these techniques has emerged, and "human gene therapy" research institutions and regulatory mechanisms already exist that are defined in these terms, all providing a ready-made jurisdiction for IGM policy makers' work. Why, then, should we seek to reach farther than this captive audience?

### *2. Second Thoughts about Retaining a Narrow Domain*

On the other hand, most policy makers are not interested in policies that neglect to address major sources of their primary problem, even if those policies are easier to implement and police. If our core concerns about creating inheritable genetic changes in children are being raised first at the scientific side doors we previewed above, intentionally limiting our gaze to germ-line gene transfer techniques simply because they are what we have always expected to discuss seems obtuse. In fact, given the pace and unpredictability of science, chaining our policy to any specific current technology is probably unwise. If there is no good reason why our policies should be tied to a specific technique for making changes in our children's genes, it would probably be prudent to craft as technologically neutral a policy as possible.

### *3. Casting the Wide Net of "Genetic Control"*

One way to accomplish this neutrality, of course, would be to adopt the second definitional option, and simply be as inclusive as possible in what we mean by "germ-line interventions" for regulatory purposes. One important element of our moral concern about germ-line gene transfer has always been the control that it would give us over the genes of our offspring. What does it mean, morally, to

be able to shape our children at the genetic level?[10] Given this quandary, why not just stipulate that any human intervention in the flow of genes from parents to children should count as a "germ-line" intervention for the purposes of our policy, and prepare ourselves to address whatever techniques that net snares?

One of the historical features of the "germ-line" concept that makes this option seductive is its overlap with the notion of a "blood line." The blood line is a traditional metaphor for the relationships within human lineages, and plays on the (now discarded) theory that the actual blood of both parents mixes together to provide the blood of their offspring. Weismann's germ plasm was also supposed to work this way, as a kind of cellular blood, and the germ-line concept still carries the connotation of being a continuous stream of living matter that weaves its way through the generations in a family. This suggests that any technique that interrupts, adds to, or changes the content of that intergenerational gene stream could count as a "germ-line intervention" and fall within the jurisdiction of our IGM policy, regardless of the methods it uses to achieve its effects. At its broadest interpretation, the category would include not only biomedical interventions like preimplantation and prenatal genetic screening, adult genetic counseling, donor insemination, oocyte sperm injection, and surgical sterilization, but also other social practices with similar effects on the next generation's gene pool, including celibacy, contraception, incest taboos, and matchmaking.

*4. Second Thoughts about the Wide Net*

Now the net seems to have caught too much. Can we really expect IGM policy makers to address, as a matter of professional, institutional, or public science policy, the whole range of human practices that influence which genes we pass on to our children? To what audience would such policies be addressed? Given our social commitments to protecting a "sphere of privacy" around many of these reproductive practices (fueled in part by our historical experience with eugenic policy making), it would seem far too intrusive to suggest that, even in an ideal world, IGM policy makers should be empowered to police our private lives to this extent. Relying too much on the "blood line" connotations of the germ-line concept seems to have produced a policy domain too large to implement with either a clean conscience or any hope of success, effectively sabotaging the whole effort.

*5. Returning to the Narrow Definition for New Clues*

This suggests another look at the arguments behind the first option. In addition to the concern over genetic control, there have also been other impor-

tant moral concerns in the discussion of germ-line gene transfer, and these do help further delimit the IGM policy maker's distinctive domain. First, the fact that germ-line gene transfer would be a new biomedical intervention, rather than a nonscientific social practice, is significant. The IGM policy maker's problem has been operationalized as a *science* policy problem concerned with which biomedical advances scientists should be encouraged (or allowed) to pursue on society's behalf. As important as it is to construct a complete ethical analysis of the issue, the limits of parental liberty to attempt to influence their children's genes has not been the boundary that IGM policy makers have been asked to police. Rather, their question has been whether it would ever be appropriate, from the point of view of society, the biomedical community, or the individual scientist, for scientific research to be brought to the aid of those parental attempts. Whether or not there emerges "consumer demand" for increased genetic control, in other words, is this a direction which a responsible society or scientific community should be willing to explore? Limiting their domain this way obviously makes IGM policy makers' task more manageable and their audience more obvious. But it also reflects an important moral commitment that is worth preserving. Despite the value we place on "scientific freedom," we accept the policing of science by scientists, institutions, and society to a degree that we will not accept for private reproductive practices. In part, we accept this increased oversight as a function of society's investment in science. To the extent that science is conducted with public support and on behalf of the public, society is justified in helping to shape its pace and priorities. The more convincing case for such oversight, however, is the increasing power of science and its concomitant risks of public harm. Compared with the genetic risks posed by our private reproductive decisions, the potential harms of genetic science are both less contested and more threatening, if only because they can be replicated so precisely and reliably in multiple subjects.

This point provides a new reason for IGM policy makers to tailor their domain a bit more closely to the paradigm of germ-line gene transfer after all. Slavishly restricting our policy to one set of biomedical techniques for administrative convenience still seems imprudent. However, limiting its domain to the policy problems created by the prospect of better biomedical tools in general seems justified, because doing so reflects a core moral concern to minimize the special risks of science that do not arise for other social practices that affect the human gene pool.

### *6. The Special Risks of Genetic Science*

If minimizing the special risks of genetic science is important enough to warrant limiting the domain of IGM policy making to *biomedical* interventions that create inheritable changes in human beings, it is worth exploring these risks a bit further. So far, the domain that our analytic dance has suggested for IGM policy making would cover all biomedical interventions that hold out the prospect of increasing our ability to control genetic traits of the next generation. This still cuts a broad swath for policy makers, including all of our genetic screening practices and many of the new techniques in reproductive medicine. Is there any good reason to delimit the domain further, in terms of the core moral concerns that germ-line gene transfer techniques have hitherto flagged?

It is true that our discussions of the special risks of germ-line gene transfer techniques have been selectively focused. For example, unlike our concerns over the false promises of somatic cell gene "therapies," there has been relatively little concern about the risk that, after getting everyone's hopes up, germ-line gene transfer techniques simply will not work, leaving us to continue to cope with the genetic roulette we already impose on our children. Instead, our concerns have either been about the prospect that these techniques will succeed, raising our questions about the morality of genetic control, or that they will backfire and inflict subtle new genetic harms on the next generation. The latter point is important, because it suggests a moral concern that does distinguish some biomedical interventions, like germ-line gene transfer and its cousins, from others, like genetic screening and sterilization, which do not raise the risks of iatrogenic genetic harm. It highlights the fact that we are primarily concerned in IGM policy making about the dangers and injustices of making genetic changes in children *who are expected eventually to pass on those changes,* not with the dangers and injustices of selecting who will be born. Intergenerational screening techniques, while they do raise the issue of genetic control, do not impose on their survivors additional risks of inheritable genetic harms, because those techniques do not make genetic changes in their survivors at all. As a result, for screening techniques, we do worry about the risk of false negatives and false positives, because for their purposes the perpetuation of our genetic roulette is the worst health outcome they face. Biomedical interventions that also pose the risk of insinuating new genetic health risks into their surviving

patients face the next level of difficulty in terms of our concerns for the special risks of science, and in doing so seem to warrant the special attention of policy makers charged with policing the public safety of our genetic science.

### *7. Reframing the Policy-Making Domain*

Using the deficiencies of the first two domain-defining options for IGM policy makers to probe our intuitions about the core moral concerns flagged by the concept of germ-line interventions has already produced a sketch of the third alternative. In short, the kinds of intervention that should fall within the IGM policy maker's purview are those that raise the three core issues we have uncovered so far: (1) they should be interventions that hold out the prospect of increasing our control over the specific hereditary traits of the next generation if they succeed (i.e., interventions that modify the set of genes our offspring carry and will pass on to their children in turn); (2) they should be interventions that raise the issues of scientific responsibility (i.e., biomedical interventions, rather than nonscientific social practices); and (3) they should be interventions that pose the risk of creating iatrogenic genetic harms if they fail (i.e., interventions that make inheritable changes in the genes of surviving offspring, rather than interventions that simply select among offspring on the basis of their naturally inherited genes).

The easiest way to assess the merits of our third option is to apply it to the range of new approaches to creating genetic changes in human beings that we previewed in our introduction. These new interventions raise three kinds of jurisdictional questions for IGM policy makers, which concern the *effects, targets,* and *means* of the interventions in question. Examining each of these, in turn, will raise the remaining definitional considerations that we think will soon become important for any adequate IGM policy making.

### *8. Just Intentional or Also Inadvertent IGM Effects?*

Some somatic cell gene therapy protocols, like the in utero experiments proposed in 1998, pose a risk of inadvertently transducing germ-line cells in their subjects and transmitting iatrogenic genetic defects in the process.[11] Should they be included within the jurisdiction of our IGM policies? After all, there are other forms of biomedical research, such as radiotherapy or chemotherapy research, in which we accept some risk of harmful, inheritable, iatrogenic mutations. These risks do not ordinarily lead us to consider such research as a form of "germ-line genetic engineering." However, we do use the equivalent risks of insertional mutagenesis to justify our zero-tolerance attitude toward the ia-

trogenic genetic risks in current somatic cell gene transfer research. Is there something special about this kind of iatrogenic risk, or the way gene transfer techniques create them, which differentiates both deliberate and inadvertent germ-line transformations from other mutagenic interventions for IGM policy purposes?

The answer is yes, and applying our criteria shows where this special difference lies. For while mutagenic interventions like chemotherapy can pose genetic risks, they do not offer improved ways to control the genetic changes they create. Insofar as they do not raise concerns about increasing our control over the genetic makeup of our offspring, inadvertent IGM-producing interventions do not belong within the purview of the IGM policy maker. Gene transfer strategies like those involved in the in utero protocols also involve unknown germ-line genetic risks that are analogous to the risks of chemotherapy. However, it is also plausible to ask, as French Anderson does, whether a successful (i.e., unintended but *nevertheless adequately* controlled) germ-line transformation should count as a risk of or a serendipitous benefit from such research.[12] The prospect of making controlled changes is distinctive here, because it is what opens the intervention to being interpreted as one step in the research process toward a full-fledged biomedical ability to control the traits of our offspring. Because inadvertent IGM-creating interventions might well be a side door to such increased control, they do belong within that purview.

### *9. Nuclear or Mitochondrial Targets of Intervention?*

One of the interesting discoveries in the twentieth-century scientific exploration of the "germ plasm" has been the finding that human genes reside in more than one structure within the cytoplasm of human cells. Most genes are bound up in the chromosomes that constitute the cell's nucleus. In the future, however, some genes may remain outside the nucleus on "artificial chromosomes" specifically designed as stable, self-replicating vectors for genetic interventions.[13] If these artificial chromosomes were introduced early enough in development to be replicated in the germ-line cells, they would be performing the same function as viral vectors that integrate new genetic inserts into the nuclear DNA, and they would indisputably be considered "germ-line genetic interventions." In fact, clinical interventions have already been performed in humans that follow this format, although the vehicles they use to transport the extranuclear genes are perfectly natural mitochondria, the organelles that help produce energy for cellular respiration. Mitochondria carry their own DNA,

and mutations in these genes, just as in the nuclear genome, can cause serious disease. New micromanipulation techniques have made it possible to compensate for mitochondrial genetic diseases in two different ways. We can now either transplant chunks of healthy cytoplasm (carrying functional mitochondria) into the cytoplasm of a diseased fertilized egg, or transplant the nucleus of a diseased fertilized egg into an enucleated but mitochondrially healthy egg. Obviously, in both cases, these transplantations would be performed early enough in development to be propagated through the resulting individual's germ-line cells. Should these subcellular "organelle transplants" fall under the purview of our IGM policies, just like the germ-line introduction of artificial chromosomes would?[14]

Under our analysis of the issues that our IGM policies are supposed to address, it is hard to see how these techniques could be excluded from consideration. In the first case, the importation of new mitochondrial DNA (mDNA) into an oocyte will produce a new hybrid genome that will persist throughout the life of the subsequent child, carrying with it whatever specific new traits and subtle genetic risks are encoded in it. The fact that the mitochondrial genome is too small to raise these issues in very dramatic ways does not mean it should be excluded from our IGM policies, any more than minimal risk clinical research should be ignored by our human subjects policies. At most, it suggests that there may be degrees of urgency within our IGM policy domain, allowing policy makers to prioritize their efforts according to the potency of the intervention.

The case of in vitro oocyte nuclear transfer (IVONT) is made more complicated by our tendency to locate a fertilized egg's identity in its nuclear genome, but the issue turns out to be very similar. Recall that our core moral concerns—our worries about genetic control and iatrogenic harm—betray no prejudice for one kind of cellular DNA over another. Thus, it does not matter if one argues that IVONT involves an egg receiving new mitochondrial DNA or an egg receiving a new nucleus: either way, a human germ-line cell has had part of its genome—either its mitochondrial or nuclear part—replaced in a way that will be inherited by its descendants.

On the other hand, except for the artificial chromosome, all of the interventions we have discussed here employ relatively gross cellular manipulations, not the recombinant DNA–based gene transfer techniques of our paradigm case. Is this a clue that it would be another mistake of overinclusiveness to sweep them into our IGM policies? Do the different biomedical means of

effecting these inheritable, potentially risky genetic changes raise different core moral concerns? If not, why not?

*10. Molecular or Cellular Means of Intervention?*

Again, most discussions of IGM policy making to date have assumed that the topic is part of our effort to ensure the safety of recombinant DNA (rDNA) technology.[15] This assumption reflects the history of this debate in the United States, and its relative isolation from the growth of our ability to manipulate human cells and their parts in other ways. But now that it is possible to "hybridize" or fuse many different cell types and to transplant subcellular components from one cell to another, and even manipulate particular protein molecules (oligonucleotides) to induce gene repair, there are many other ways to introduce or alter genes in germ-line cells that do not depend on the recombination of nucleic acid molecules. Should these other techniques also be governed by our IGM policies?

If our policies are framed against the core moral concerns we have identified, the answer must be affirmative. As we have seen, one of the core concerns that the prospect of germ-line gene transfer flags is that the health of the engineered and their progeny will be compromised by the creation of inheritable iatrogenic harms. For gene transfer interventions, this concern has focused on the "insertional mutagenesis" risks characteristic of rDNA research, which the cellular techniques do not pose. However, the cellular and protein chemistry techniques do pose other risks of creating inheritable genetic defects: risks of accumulating too many chromosomes (polyploidy) in cell fusion, for example, or the risks of genetic regulatory dysfunctions in oligonucleotide therapies. If we are interested in developing comprehensive policy to control the development and use of techniques capable of creating inheritable genetic changes in humans, it seems arbitrarily narrow to limit our focus to iatrogenic genetic risks of one type and not the other. At most, perhaps a hierarchy of risks is required, providing policy makers a scale for measuring the comparative priority of different emerging technologies.

Of course, it would be a mistake to hope that defining the domain of our IGM policies in terms of moral issues rather than biomedical methods will eliminate all jurisdictional controversies for IGM policy makers. No matter what one's definitional strategy, there will be biomedical techniques and clinical situations that challenge it. For example, consider the status of somatic cell nuclear transfer (SCNT) under our criteria. At first glance, SCNT might look

more like genomic *repetition* or *replacement* than like genomic *modification.* After all, when the nuclear DNA from the host egg is replaced by the foreign somatic cell's nucleus, it does seem as if the egg has been given a completely new genetic identity. But that, of course, is to ignore the (far greater in weight and number) mitochondrial portions of that new zygote's genome, which persist unreplaced in its cytoplasm. In terms of the genomic identity of the whole cell, perhaps SCNT functions more like a heart transplant than a brain transplant, as biologists like Richard Lewontin would have us believe.[16] Not only does SCNT vividly raise the same core moral concerns about controlling the genetic shape of our children that traditional germ-line policies were crafted to address, it also poses clear risks of iatrogenic genetic harms (e.g., telomeric insufficiency), much like the risks in germ-line gene transfer protocols. If the egg is considered the cell transformed by the transplant, modifying its genome in an inheritable way, then perhaps SCNT might indeed fall within the purview of our IGM policies.

By the same token, of course, it might also be argued that intracytoplasmic sperm injection (ICSI) should also fall within the jurisdiction of our IGM policies. This might be so to the extent that it increases our genetic control by supplying a specific new genome to an egg that the resulting conceptus will perpetuate throughout its life and bequeath to his or her own progeny, including whatever inborn genetic defects (like the mutation responsible for its father's original infertility) it carries.

But again, the IGM policy-making discussion has never been about regulating the slings and arrows of natural genetic misfortune, and some might respond that the natural genetic defects perpetuated by ICSI are not iatrogenic errors introduced by the intervention itself in the same way as are insertional mutations caused by attempts at gene transfer. This returns us again to the point that our IGM policy making is supposed to help govern biomedical research and the technological interventions that research yields, not the dynamics of the natural world. From that point of view, the status of biomedical interventions that clearly increase our genetic control over the next generation, but do not clearly create the risk of iatrogenic genetic harms in the process, like ICSI or even the preimplantation disaggregation of embryos for genetic diagnosis, will have to remain ambiguous even by the moral criteria of the third option. But so it goes: no policy is going to be able to establish airtight categories in this fluid an environment, and at least it is helpful to be able to put these interventions on a spectrum of policy-making priorities.

## Planks in a Definitional Platform

What kinds of biomedical research should an adequate IGM policy cover? To start with, our dance through the possibilities suggests that the hundred-year-old jargon we currently use to frame the domain of those policies may no longer be adequate for our needs. Others have noticed how the label given to any genetic intervention—whether it is called *manipulation* or *engineering*, *therapy* or *research*—can frame its policy discussion.[17] We think the label *germ line* can also be distracting, by suggesting blood-line notions of gene flow, restricting our focus to rDNA techniques involving nuclear genomes and suggesting issues that do not turn on the controlled nature of the genetic changes that concern us. Instead, we would try to define the policy domain in a way that would highlight the core issues at stake, along the following lines.

Our approach is designed to govern all the technologies, techniques, and interventions capable of creating IGM in human beings, a set of biomedical tools we will call "IGM techniques." We include as IGM techniques any biomedical intervention that can be expected to enable us to modify the genome that the subject of the intervention can transmit to her or his offspring selectively.

As we suggested in the beginning, arriving at a definition for policy purposes often involves decision making that precedes the substance of the policy itself. While we think our definitional exercise has not prejudged the issue of creating inheritable human mutations entirely, it has clearly brought us to some conclusions about those interventions we think should be within the purview of IGM policy makers.

1. IGM policy makers should attend to biomedical interventions that create inheritable genetic changes in surviving subjects, rather than attempting to address other social practices or biomedical interventions that influence the genetic makeup of the next generation.
2. Policy makers should allocate priority against two scales: the degree to which a given intervention promises to increase our ability to control the genes of our offspring, and the degree to which it poses risks of severe iatrogenic genetic harms to our offspring.
3. Beyond these relative rankings, IGM policy makers should be concerned about inheritable modifications whether or not the intervention modifies nuclear or extranuclear genomes and relies on molecu-

> lar genetic or other technical strategies, and even whether or not the modification is a side effect or the central purpose of the intervention.

Taking this approach will mean that germ-line gene transfer strategies remain the paradigmatic subject for our IGM policies, but at the same time, our ability to address the IGM techniques now seeking entrance at our scientific side doors will improve. While some genetic interventions (e.g., prenatal diagnosis and matchmaking) will clearly fall outside the purview of IGM policy makers using these criteria, and others (such as SCNT and ICSI) will be debatable, a significant new set of interventions, from oligonucleotide therapies to artificial chromosomes and mitochondrial transplants, will now need, at varying levels of priority, to become subjects for our science policy oversight.

NOTES

1. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *Splicing Life: A Report on the Social and Ethical Issues of Genetic Engineering with Human Beings* (Washington, D.C.: The Commission, 1982).

2. Cf. Eric Juengst, "The NIH 'Points to Consider' and the Limits of Gene Therapy," *Human Gene Therapy* 1 (1990): 425–33.

3. August Weismann, "Die Continuitat des Keimplasmas als Grundlage einer Theorie der Verebung," *Aufsatze uber Verebung und Verwandte Biologische* (Fragen, Jena, Germany, 1885). (Translated in August Weismann, *Essays upon Heredity and Kindred Biological Problems* [Oxford: Oxford University Press, 1891].)

4. Daniel J. Kevles, *In the Name of Eugenics: Genetics and the Uses of Human Heredity* (New York: Alfred A. Knopf, 1985), 19, 70–71. On page 67 of his book, Kevles quotes a representative exhortation from eugenicist Michael Guyer, reminding parents that "their one sacred obligation to the immortal germ plasm of which they are trustees is to see that they hand it over with its maximal possibilities undimmed by innutrition, poisons or vice" (Michael Guyer, *Being Well Born: An Introduction to Eugenics* [Indianapolis: Bobbs-Merrill, 1916], 194).

5. It is interesting that in many discussions "germ-line gene therapy" is initially defined as interventions directed at the "germ cells" (e.g., the sperm and egg), but then described in terms of strategies that involve transforming embryos. For example, see the U.S. Office of Technology Assessment report, where its says simply: "gene therapy might be performed in either the germ cells (sperm, egg cells or the cells that give rise to them) or in somatic cells (cells that comprise all other body tissues)" (*Human Gene Therapy: A Background Paper* [Washington, D.C.: U.S. Government Printing Office, 1982], 6). This rhetorical move plays off the vestigial colloquial use of the "germ cell"

language to refer to gametes, and uses it to frame the discussion in a manner that is less ominous than defining it in terms of engineering embryos. As Fowler et al. note: "Gametocyte therapy's great advantage . . . is that it does not expand the circle of patients in the clinical situation. Gametocyte therapy would solve the client's reproductive health problems in their own bodies, before the need to worry about their offspring arises. Thus, adults could knowingly assume the clinical risks they face in receiving the intervention, and no research subjects would be required to involuntarily accept the risks that the first human trials would inevitably involve" (Greg Fowler, Eric Juengst, and Burke Zimmerman, "Germ-line Gene Therapy and the Clinical Ethos of Medical Genetics," *Theoretical Medicine* 10 [1989]: 151–65).

6. Jose B. Cebelli, Steve L. Stice, Paul J. Golueke, Jeff J. Kane, Joseph Jerry, Cathy Blackwell, F. Abel Ponce de Leon, and James M. Robl, "Cloned Transgenic Calves Produced from Nonquiescent Fetal Fibroblasts," *Science* 280 (1998): 1256–58.

7. Melissa A. Rosenfeld, "Human Artificial Chromosomes Get Real," *Nature Genetics* 15 (1997): 333–35.

8. J. Cohen, R. T. Scott, T. Schimmel, J. Levron, and S. M. Willadsen, "Birth Following Transfer of Enucleated Donor Oocyte Cytoplasm into Recipient Eggs of a Patient with Recurrent Poor Embryo Development and Failed Implantation," *Lancet* 350 (1997): 186; J. A. Barritt, C. A. Brenner, H. Malter, and J. Cohen, "Mitochondria in Human Offspring Derived from Ooplasmic Transplantation," *Human Reproduction* 16 (2001): 513–16.

9. Cf. E. Parens and E. Juengst, "Inadvertently Crossing the Germ Line," *Science* 292 (2001): 397.

10. Sometimes the concern about control is deontological; that is, too much control is, in itself, bad for humans. More often, the concern is about undesirable consequences, such as: (1) the widening of the gap between the haves and have nots, or (2) the promotion of or complicity with so-called suspect norms of normality or perfection. See Erik Parens, ed., *Enhancing Human Traits: Social and Ethical Implications* (Washington, D.C.: Georgetown University Press, 1998).

11. Meredith Waldman, "NIH Launches Discussion of *In Utero* Gene Therapy," *Nature* (1998): 420.

12. See National Institutes of Health, *Prenatal Gene Transfer: Scientific, Medical, and Ethical Issues,* a report of the Recombinant DNA Advisory Committee, NIH Publication 00-4720 (U.S. Department of Health and Human Services, 1999).

13. Huntington F. Willard, "Chromosome Manipulation: A Systematic Approach toward Understanding Human Chromosome Structure and Function," *Proceedings of the National Academy of the Sciences USA* 93 (1996): 6847–50.

14. Cf. E. M. Berger, "IVONT and the Trojan Horse," *Politics and the Life Sciences* 17 (March 1998): 13–14; D. B. Resnik and P. J. Langer, "Human Germline Gene Therapy Reconsidered," *Human Gene Therapy* 12 (2001): 1449–59.

15. Two exceptions to that generalization: David S. Rubenstein, David C. Thomasma, Eric A. Schon, and Michael J. Zinaman, "Germ-line Therapy to Cure Mitochondrial Disease: Protocol and Ethics of In Vitro Ovum Nuclear Transplantation," *Cambridge Quarterly of Healthcare Ethics* 4 (1995): 316–39; and Andrea L. Bonnicksen, "Transplanting Nuclei between Human Eggs: Implications for Germ-line Genetics," *Politics and the Life Sciences* 17 (1998): 3–10.

16. Richard Lewontin, *Biology as Ideology: The Doctrine of DNA* (New York: Harper-Perennial, 1993).

17. Keith Boone, "Bad Axioms in Genetic Engineering," *Hastings Center Report* 18 (1988): 9–13; Nancy King, "Rewriting the 'Points to Consider': The Ethical Impact of Guidance Document Language," *Human Gene Therapy* 10 (1999): 133–39.

CHAPTER THREE

# Approaches to Gene Transfer to the Mammalian Germ Line

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The application of the rapidly emerging techniques of gene therapy to heritable human genetic modification is inevitable. During the past several decades, a number of such methods have been developed and successfully applied to germ-line modification in rodents and a number of larger mammals. These advances have established clearly that foreign genetic elements introduced into mammals can not only produce valuable models for studying human disease but also prevent the development of genetic disease. Unfortunately, the low efficiency of these current methods along with a variety of additional technical problems, such as the need for breeding and selection of founder ("parent") animals to achieve the desired final genotype and phenotype, make application of current methods to human beings impractical and morally unacceptable. It is nevertheless likely that future improvements in the efficiency and targetability of current methods of gene transfer and the development of gene correction and replacement methods will eventually be applied to attempts at germ-line modification in humans. In principle, foreign genetic elements might be introduced into the germ line of an organism by genetic modification of the gametes themselves, by genetic modification of the fertilized egg, or by gene

transfer into the embryonic cells that eventually produce gametes. The greatest success during the past several decades has been through the latter two mechanisms, and has been made possible by the identification and use of multi- or totipotential embryonic stem cells that can be maintained indefinitely in culture, genetically modified by readily available methods, and then used to reconstitute living progeny. This advance suggests that similar germ-line modification may become technically feasible, although a number of logistical, policy, and ethical factors will continue to make application to human beings difficult.

## Gene Transfer into Gametes

At first glance, the reproductive cells themselves (i.e., spermatocytes and oocytes) would seem to represent potentially attractive targets for genetic modification. Nevertheless, the absence of convincing success in direct genetic modification of these cells probably reflects both the lack of emphasis on the gametes as gene modification targets as well as technical problems that might impede their heritable genetic modification. There have been very few studies aimed at gene transfer into gametes in vivo, although one unpublished study has very recently demonstrated virus vector–mediated transfer and expression of foreign reporter genes (gene identifiers of other genes) into mouse spermatocytes, again without evidence for germ-cell transmission to progeny.[1] No similar studies have been reported in the female. These studies lend support to the likelihood that further improvements in vector delivery and targeting will eventually succeed in delivering functional genes in vivo to the germ cells in ways that permit functional transfer to subsequent generations. At the moment, those techniques, while conceivable, are not on the immediate horizon.

Spermatocytes are, of course, readily available, but there is virtually no information on the ability of any of the currently available gene transfer vectors—virus vectors, nonviral reagents such as lipid-DNA complexes (liposomes), or other materials—to introduce foreign genetic elements into these cells. Furthermore, the application of gene transfer methods to sperm for germ-line therapy purposes implies either that the efficiency of gene transfer must be exceedingly high to ensure genetic modification of virtually all sperm in a sample or that rare genetically modified spermatocytes can be selected from the mass of nonmodified cells to ensure that resulting offspring are derived from the genetically modified sperm cell. The most relevant results to

date with respect to the genetic modification of sperm have been provided by studies not with mature sperm themselves but with cultured lines of spermatogonia, the stem cell precursor of fully matured spermatocytes. These cells can be grown readily and indefinitely in culture, and then genetically modified and introduced into the testis of a recipient animal where they can undergo differentiation to mature sperm. For instance, mouse spermatogonia have been introduced into rat testis and the recipient rat was then able to produce functional mouse sperm.[2] Farther away technically, but by no means inconceivable, is the development of methods for efficient targeted delivery of foreign genetic elements to the developing spermatocytes in the testis in vivo. At the present time, such targeting methods are far from reality.

In contrast, although oocytes are not as accessible as spermatocytes, they can be readily retrieved from suitably prepared females by the minimally invasive method of laparoscopy used for in vitro fertilization (IVF). Despite the fact that the susceptibility of human oocytes to most gene transfer vectors has not yet been studied thoroughly, there is no reason to expect that suitably designed viral or nonviral vectors will be unable to carry out gene transfer into oocytes, possibly as part of the IVF process. As in the case of the testis, efficient delivery of therapeutic genetic elements to the oocytes in vivo is not feasible at the present time, but it is likely that suitable methods for in vivo delivery of genes to the ovary will eventually be developed.

Will the delivery of genes or other genetic elements to gametes, either in vivo or in vitro, have useful applications for prolonged germ-line genetic modification? It should be remembered that mature, fully differentiated oocytes and sperm are haploid and carry only single copies of each chromosome pair. Furthermore, unless a genetic modification in these cells were to occur at the specific defective loci in the target genome ("homologous recombination" or "mismatch repair") to produce a true sequence correction or replacement of the defective gene, the genetically modified gamete would carry and transmit both the therapeutic as well as the original mutant gene to a resulting zygote. In fact, most gene therapy models entail addition of new genes to an existing defective genome. Methods for true gene replacement or correction of endogenous mutations by homologous recombination or mismatch repair are only in their earliest stages of development. Spermatogonia are diploid cells and gene transfer into them with present techniques would also result in the addition of a normal allele into a site on the genome different from its ordinary position in the genome without replacing the defective gene. The result of

such an addition, in the absence of sequence correction or replacement of the disease-related element, would be the unimpaired transmission of a defective gene to a zygote and to subsequent generations. The correction of a disease phenotype would depend on the co-segregation of the therapeutic genetic element with the disease-related element. However, because of the untargeted random integration of the therapeutic element and independent segregation of the chromosomes and meiotic cell division (reduction of chromosome number required in production of gametes) of genetically modified spermatogonia, the two markers would not be inherited together and therefore the intended germ-line correction would not be transferred to all subsequent generations. For these reasons, stable, efficient, and heritable germ-line modification through the gametes or their precursor stem cells does not seem to be feasible with current methods, and only direct correction or replacement of the endogenous defective gene would make this approach broadly attractive.

Methods for the introduction of foreign genes into the mammalian germ line have been practiced on a routine basis since the introduction of "transgenic" mouse technology by Gordon and Ruddle in 1982.[3] Since that time, the method has become one of the mainstays in modern cellular and molecular genetics and has been used successfully to produce innumerable animal models for human genetic disease and to understand many aspects of mammalian gene regulation. The technology, while not simple, is readily learned and implemented in most modern laboratories and research institutions. As generally practiced today in mice, the methodology involves injection of a purified gene (or other DNA segment) or genetic element encoding a foreign gene into one of the pronuclei in a fertilized mouse egg, followed by implantation of the genetically modified egg into a hormonally treated ("pseudopregnant") female who is receptive for embryo implantation. If successful, the injected genetic material becomes integrated, although into a nonspecific site, in the genome present in the pronucleus, and subsequent development of the embryo leads eventually to animals heterozygous for the added new gene. The technology is inefficient, and even in the most experienced hands, produces heterozygosity for the new gene in no more than several percent of resulting founder animals. The tissue distribution of transgene expression depends on a number of factors, including the regulatory elements introduced with the gene and position effects related to the site of integration. Alternatively, transgenic mice can be produced through the use of virus vectors to infect preimplantation embryos in vitro with subsequent implantation as above.

The introduction of a foreign gene into these transgenic mice is followed by not only stable and heritable gene expression but also permanent correction of genetic defects in the mouse. Early examples of such stable prevention of genetic disease in the mouse include correction of the genetic defects responsible for growth hormone deficiency in dwarfism, myelin basic protein deficiency in the neurologically aberrant "shiverer" mouse, apoA1 and apoE deficiency in hypercholesterolemic mice, hypoxanthine guanine phosphoribosyltransferase (HPRT) deficiency in the mouse Lesch-Nyhan model, and many other disorders. It is, therefore, clear that expression of a foreign gene in the germ line can cure a genetic disease, at least in the mouse.

In the absence of major improvements in efficiency and genomic targeting of added genetic elements, the current transgenic methodology is not suitable for human application. With currently available techniques and tools, the added genetic material is integrated with only a very low efficiency into random chromosomal locations in the target cell genome, and the correction of a disease phenotype in the resulting zygote and subsequent generations is incomplete, inefficient, and unstable. Furthermore, the low efficiency of producing animals that transmit the added transgene in their germ line makes it necessary to identify and breed founder animals and generally to eliminate animals that do not demonstrate the appropriate genotype and phenotype. These steps are not readily applicable to human studies. As above, only sequence correction methods would avert the problems of segregation of the therapeutic gene from the disease-related gene. Even with the advent of such technology, it would be important to develop methods to ensure an exceedingly efficient method of delivering such gene-correcting or -replacing materials to the target cell to reduce the challenges of identifying appropriately modified zygotes or embryos before implantation.

Another interesting new approach to the production of transgenic animals has recently been reported that may prove to be a means of providing very large amounts of genetic information to the germ line of mice in the form of independently replicating artificial chromosomes.[4] This study reports for the first time the introduction of an extra, artificially constructed chromosome into transgenic mice and its subsequent transmission to progeny mice. It will obviously be necessary to determine the long-term developmental effects of producing a state of aneuploidy (an abnormal number of chromosomes) in an animal. While artificial chromosomes in theory may permit the inclusion of large amounts of the necessary regulatory sequences to accompany a desired new ge-

netic function in transgenic animals, such a manipulation may be accompanied by some genetic and developmental damage. There are no known states of aneuploidy in the human that are free of detectable, and in most cases very severe, genetic and developmental abnormalities.

## Embryonic Stem Cells for Gene Transfer into Embryos

A second powerful technology for introducing foreign genes into mammalian germ lines emerged in the late 1980s with the introduction by a number of investigators of methods that allowed the precise replacement of one sequence in the genome by another related sequence through targeted homologous recombination. This method permits the introduction of mutations into normal genes to produce mouse models of human disease ("knockout" mice) or to introduce therapeutic sequences into specified target sites in the genome to correct a genetic defect ("knockin" mice).[5] This important development relies on the availability of two major tools: (1) cells derived from the mammalian embryo that have the capacity to develop into every cell type of the adult animal (pluripotent or even totipotent embryonic cells), and (2) a site-specific recombination method for introducing foreign genetic material into such cells in a way that permits specific genes to be removed or inserted into the genome at a defined location in the genome (e.g., targeted mutagenesis through homologous recombination between the incoming genetic element and the resident genome).

The pluripotent embryonic stem (ES) cells, commonly derived from a portion of the embryo called the inner cell mass, can be grown indefinitely in culture and genetically modified by at least some established methods of gene transfer, although the efficiency of the site-specific recombination event is exceedingly low. The rare cells in which the recombination has occurred must be isolated by powerful in vitro cell selection methods and the specifically modified cells must then be amplified in culture. Although this selection capability of cultured stem cells obviates to some extent the need for highly efficient gene transfer techniques, it would nevertheless be desirable to carry out the gene transfer step as efficiently as possible since prolonged culturing always predisposes cells to a variety of chromosomal aberrations and to other changes that may predispose the cells to become tumorigenic. To date, there is very little information on the susceptibility of these stem cells to many other virus-mediated or nonviral gene transfer techniques.

The purified, genetically modified stem cells are introduced into the mouse embryo at the blastocyst stage of development, where they participate in embryo development by interspersing to varying degrees with the other pluripotent cells of the inner cell mass in the early embryo and by differentiating into cells of all tissue types in the organism, including the germ cells. At birth, the resulting mouse is a "chimera"—an animal most of whose tissues contain mixtures of cells derived from both the cells of the embryo itself and from the introduced genetically altered stem cells. For the desired genetic change to become fixed in the germ line and heritable to later generations, the genetically modified cells must contribute to the development of the germ cells of the resulting animal.

Unfortunately, the efficiency of the integration of the modified ES cells with the other cells in the mouse embryo has, until now, usually been both low and uncontrollable. This has meant that the injected stem cells do not participate in the development of all the same final cell lineages and tissue development with the same efficiency from one embryo to another in a fashion that is predictable or that can be controlled by the investigator. Most important, some animals will express the gene well in the germ cells of the resulting chimeric animals, some will do so poorly, and some not at all. It is therefore necessary to identify the founder chimeric animals that contain germ-line genetic changes and breed those founder chimeric animals to establish a new mouse strain in which the genetic change is fixed in the germ line. The initial chimeric animals are merely intermediates in the process of generating a mouse with the desired genotype and the resulting genetically modified desired phenotype. Along the way, chimeras with undesired distribution or expression of the genetic marker are expendable.

Until methods can be developed to increase vastly the participation of the injected genetically modified stem cells in embryo development or even to produce animals entirely from the genetically modified stem cells without having to introduce them into blastocysts, this chimerism phenomenon and the need to breed founder animals will remain features of the targeted homologous recombination technology for the immediate future, even in the mouse. Interestingly, a method has been reported by which mouse ES stem cells mixed with mouse embryos containing double the normal number of chromosomes ("tetraploid" embryos) could be introduced directly into pseudopregnant female mice to produce mice that contained enzyme markers derived entirely from the stem cells and not from the tetraploid mouse embryos.[6] The latter

were required only to provide those cells (trophoblastic cells) that are needed for placenta development and that do not participate at all in embryo development. Similar techniques are certainly not unimaginable in the case of human stem cells. If human stem cells could be substituted for the mouse cells, could these methods be used to create a genetically modified human germ line?

## Human Embryonic Stem Cells

Several groups have recently reported the isolation of human cells that display the properties of multipotent and possibly totipotent stem cells; that is, cells that may, under appropriate culturing and nurturing conditions, have the potential for developing into an entire new human being (totipotent) or, at least, to differentiate into all of the many different cells in an intact adult human being—nerve cells, muscle cells, skin cells, liver cells, blood cells, and so on (multipotent).[7] These human stemlike cells have included the following:

### *Inner Cell Mass Embryonic Stem Cells*

Inner cell mass ES cells were derived from the inner cell mass of a human blastocyst that was produced as part of an in vitro fertilization procedure and that was destined to be discarded.[8] They are analogous to those similarly derived from the inner cell mass of mouse embryos and that are known to form all of the tissues of a fetus (excluding the placenta, since they do not provide the required trophoblast function). Under ordinary conditions, such stem cells cannot fully support the development of a complete human embryo, although the study cited above in which tetraploid mouse embryos were shown capable of supporting embryo formation without contributing cells to the final mature mice suggests that similar manipulations might be feasible in the human.

### *Embryonic Germinal Ridge Cells*

Embryonic germinal ridge (EG) cells were derived from an aborted human fetus and have been shown to be capable of producing differentiated cells of all three major tissue types—endoderm, ectoderm, and mesoderm—when cultured with appropriate growth factors in culture.[9] While both the inner cell mass ES cells and the germinal ridge cells are known to be at least pluripotent, they are not likely to be identical in their developmental capacities. The timing for the isolation of germinal ridge cells from aborted human fetal tissue will al-

most certainly affect the state of gene expression in those cells and the extent to which genes have been turned on or off, imprinted, or otherwise regulated by genetic and epigenetic (relating to the expression and interaction of genes) mechanisms. Those factors may readily affect their ability to participate in embryo formation.

There is no reason to expect that, for the foreseeable future, chimeras would be less of a problem during similar manipulations in which genetically modified human stem cells are introduced into preimplantation human embryos. As in the case of the mouse technology, unless methods were developed to increase the participation of the modified ES cells in embryo development, most resulting human embryos produced by such methods would be chimeras, in which the distribution and expression of the added cells was variable and not readily subject to experimental control. Such embryos would, therefore, not only fail to benefit from the intended therapeutic genetic manipulation, but may instead be injured by the procedure. Not only is it uncertain whether the methods described above, by which entirely ES cell-derived mouse embryos were produced, are applicable to human ES cells, but also it is difficult to foresee conditions under which procedures designed to answer that question could ethically be performed.

### *Tissue-Derived (Adult) Stem Cells*

It is almost certain that other kinds of stem cells, either totipotential or at least pluripotential, will be found in nonembryonic tissue. It is already clear that such cells exist in several forms in the hematopoietic (blood cell formation) system, and stemlike cells or multipotential committed progenitor cells must also be present in other tissues that must regenerate throughout life (e.g., the liver, skin, lung, gastrointestinal epithelium, gonads, etc.). Convincing evidence has demonstrated that pluripotent cells in the brain are able to differentiate into neurons and other central nervous system (CNS) cells, and to participate structurally in brain development. The principal application of such tissue-derived stem or precursor cells seemed at first most likely for reconstituting cellular elements in diseased tissues from which they are derived. However, surprisingly, some early but compelling studies have even demonstrated that tissue-specific pluripotent cells may also have the capacity to differentiate into cells of other organs, as in early preliminary reports of grafted hematopoietic stem cells differentiating into skeletal muscle and myocardial myoblasts.[10]

## Mammalian Cloning Approaches

The development of mammalian cloning[11] has provided still another method for stably introducing foreign, potentially therapeutic genes into descendants of a specific individual, not by initial introduction of a new genetic element into the germ line but rather by nuclear transfer. Cloning has been carried out successfully in animal systems from the mouse to the pig. The donor nucleus can be genetically modified by any one of the methods for gene transfer before transfer into the enucleated oocyte, thereby producing a clone that expresses a specific new function that can then be transmitted through the germ line by the usual methods of sexual reproduction. While cloning successes are accelerating in a number of mammalian species, including mice, sheep, cows, and others, major technical problems remain and must be overcome before they can safely be applied to humans. The efficiency of successful cloning continues to be low, with efficiencies of only one in several hundred attempts in large animals such as sheep and cows. The derivation of the donor nucleus from a somatic cell implies the possible transfer to the cloned progeny of whatever genetic damage had accumulated in the donor cell before transfer, possibly predestining cloned animals to increased susceptibility to age-related disorders such as cancer and degenerative disease. Furthermore, the replication potential of cells in the cloned animals has yet to be fully characterized and may be altered by age-related changes in the telomeres—regions of the chromosomes that seem to serve as clocks that keep track of the number of divisions that a cell line has undergone. Early studies suggested, for instance, that cells of the cloned sheep Dolly contained somewhat shortened telomeres, implying that her cells had reduced number of replications available to them. More recent studies in cows have not confirmed that finding. It will be some time before the properties of donor nuclei and cloned animals will be well enough understood to permit studies in the human.

However, the cloning technology is now well enough established to have been combined recently with targeted gene delivery to develop a powerful new approach to IGM through a simplified and more controllable production of "transgenic" animals.[12] The method combined the use of sequence-specific gene targeting vectors to introduce potentially therapeutic genetic changes into fetal sheep fibroblasts (cells that give rise to connective tissue) followed by nuclear transfer into enucleated sheep oocytes by now-established mammalian cloning methods. Although the efficiency in this initial study of production of viable animals by this

procedure was low, it did result in the live birth of genetically modified and apparently healthy sheep containing and expressing the added genetic elements. The approach has the advantage of obviating the need for ES or EG "stem" cells, and therefore avoiding the difficulties associated with the need to produce and breed chimeric animals. The method proves that genetically modified "transgenic" animals can indeed be produced through a cloning approach, using genetically targeted somatic cells rather than ES or EG cells, and thereby potentially lowers some of the technical barriers standing in the way of human application.

## An Alternative Approach to Gene Correction

An alternative molecular technology with the potential to obviate the problems of untargeted and unstable line modification has recently been reported. The method, which still awaits confirmation and more extensive characterization, involves the delivery to defective cells of synthetic mixed ("chimeric") RNA/DNA oligonucleotides (strands of RNA/DNA base pairs) that are capable of undergoing homologous recombination with the resident genome, and therefore allow specific correction of disease-causing mutations both in vitro and recently in vivo.[13] Such a methodology would make it possible to correct human disease not merely by adding normal alleles randomly into the genome to correct the defective phenotype, but rather by correcting the underlying genetic defect by specific chemical genotypic correction of the disorder. While the efficiency of the described method has not yet been established and accepted, it is likely that such a homologous recombination approach to mutation correction will eventually be developed. Such potentially powerful sequence correction methods have the potential to replace mutant sequences with normal sequences in human zygotes or embryos far more efficiently than is possible by homologous recombination methods for modification of human stem cells. It will still be necessary, however, to develop methods to deliver these therapeutic materials efficiently to the appropriate cells.

## Potential Clinical Applications

There are several situations in which gene transfer into human embryos for the correction of disease in the embryo or fetus might eventually be desirable, whether it be for somatic or germ-line gene modification. For instance, a number of human diseases produce irreversible damage at early developmental

stages. If treatment of existing embryos or fetuses, rather than preimplantation detection, is an acceptable therapeutic goal, genetic correction will have to be carried out at appropriately early stages of embryo development or pregnancy. The recent convergence of methods in cell and molecular genetics with human reproductive technology strongly suggests that it may soon become possible to transfer genes into human embryos in ways that will make embryo modification possible. Transfer of totipotential embryonic stem cells into mouse embryos has become an indispensable tool for understanding gene function and for producing mouse models of human disease. The human equivalent stem cells might find a role in human reproductive technology and disease correction that will make germ-line modification in humans more feasible sooner than has previously been envisioned.

## Mitochondrial Disease and Ooplasm Transfer

A different approach to the treatment of diseases caused by mutations in the function of mitochondria has recently been developed. A group of reproductive biologists has shown that the transfer of cytoplasm from fertile donor oocytes into the oocytes of patients at risk for transmitting mitochondrial disease can prevent the genetic defect in the recipient oocytes through the generation of mixed populations of mitochondria in the resulting offspring.[14] Several dozen apparently healthy children have been born through the application of this procedure, and the investigators have indicated that such methods could be considered to represent successful inherited germ-line modification. Because no recombinant DNA technology was involved in these studies, these experiments did not go through the federal regulatory and review processes at the Food and Drug Administration (FDA) and National Institutes of Health (NIH) that would have been required for other kinds of gene transfer studies. It is not clear at the moment whether such a genetic change is stable after the first generation and whether the oocytes from a female child resulting from such a manipulation would contain and transmit mixed populations of mitochondria and therefore continue to prevent mitochondrial disease in later generations.

## Summary

Technical approaches to human germ-line genetic modification and ethical justifications for the eventual genetic correction of human disease can be

imagined. The recent identification of human embryonic stem cells opens potential new techniques for introducing foreign genes stably into the human genome for germ-line transmission. However, this potential application to the human of the two principal techniques for established germ-line modification as used in the mouse is, and will continue to be, hampered by major technical limitations, including inefficiency, nonspecificity, and the need for breeding and selecting founder animals. Over and above these technical impediments, convincing clinical indications are far from obvious and the risk/benefit ratio not convincingly low. These all indicate that, with today's technology, such applications in the human would seem to be unjustifiable and impermissible.

### *Transgenic Technology*

The "traditional" transgenic animal approach is hampered by severe inefficiency, the need for breeding and screening of founder animals, and the heterozygosity associated with integration of the foreign gene into only one member of a chromosome pair. A success rate of no more than approximately 10 percent in generating transgenic founder animals is not sufficient for human application. Obviously, the need for founder breeding and the long human generation time and unpredictability of the distribution of transgene expression are also not suitable, either technically or ethically, for human use. A recently reported modification of viral gene transfer methods to early mammalian embryos promises to increase the efficiency of transgenesis. The method uses lentivirus vectors to deliver foreign genes to single-cell mouse or rat embryos and not only has resulted in extremely high levels of gene transfer but also demonstrated transgene expression in resulting live mice or rats as well as in their subsequent progeny.[15]

To date, no methods are available to ensure integration of an added gene into the same and appropriate sites on both chromosomes in a pair, although continuing improvements in vector design and future advances in site-specific integration may eventually make such an event possible and, over a prolonged period, permit 100 percent specific homozygous genetic changes. Until that happens, half of the offspring of founder transgenic animals will not carry the therapeutic or otherwise modifying gene. For the foreseeable future, the problems associated with inefficient delivery of the oligonucleotides, the resulting heterozygosity at best, and the need for breeding founder animals will prevent application of transgenic technology to correct human genetic disease at the

early embryonic stage at all, let alone the possibility of achieving a germ-line correction by this method.

### *Stem Cell Methodology*

The identification of human embryonic stem cells does not resolve many of the issues associated with their potential application in the reproductive setting for germ-line gene therapy or other forms of genetic modification. The current technical limitations of inefficiency, unpredictability of participation of the cells in embryo development, and the assured resulting chimerism would seem to stand in the way, technically and ethically, of any attempts to produce a genetically altered human being by this method. To avert this chimerism problem, it would seem to be necessary to develop methods to produce a new organism derived entirely from the donor stem cells. This has been accomplished in the mouse by creating an early embryo that is incapable of development past the four-cell stage, but that is capable of supporting the full development of inserted ES cells. It would be unwise to assume that the same event could not occur in the human after introduction of human ES cells into a similarly prepared human embryo followed by implantation by standard IVF methods into a female to create a new pregnancy, with genetic parents defined by the origin of the ES cell. However, as in the mouse, the product of that pregnancy would in most cases be a chimera.

If the stem cells are meant to correct a genetic disorder and must therefore be modified genetically by targeted homologous recombination methods, the efficiency of the genetic change would be expected to be exceedingly low, on the order of one specific corrective event in many thousands of stem cells, as is true in the mouse. That would require prolonged culture in vitro under selective conditions, followed by extensive proof that no inadvertent genetic changes or chromosomal anomalies have been introduced during the in vitro period. Furthermore, the frequency and extent of chimera formation with such cells would be very low, as is true of the products of homologous recombination-based knockout germ-line modification with ES cells in the mouse. As in the case with mice, human chimeras would have to be identified by screening, and would then require breeding to produce a genetically modified human with a heritable genetic change. At the present stage of technology development and understanding, the use of human stem cells does not provide relief from the technical problems associated with introducing foreign genetic information into mammalian embryos.

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CHAPTER FOUR

# Scientific Methodologies to Facilitate Inheritable Genetic Modifications in Humans

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The methodologies described in this chapter are being developed primarily to facilitate somatic cell therapy or improve transplant technologies in humans. However, when fully developed, they may be used to facilitate inheritable genetic modifications in humans.

The scientific hurdles facing human germ-line intervention are similar to those in somatic gene transfer research and include methods for (1) introduction of the corrected gene into the target cell, (2) integration of the gene into the recipient genome, and (3) proper expression of the introduced gene. The different cell types in humans conducive to germ-line intervention are germ cells and their precursors; ova, sperm, and spermatogonial stem cells, respectively; zygotes, fertilized eggs at the single-cell stage; and pluripotent cells, like embryonic stem cells that have the potential to develop into various cells of the adult.

## Methods for Introducing DNA into Cells

### *Viral Vectors*

Viruses have an innate ability to infect cells, a feature manipulated in their use as vectors for gene therapy. Viral vectors used currently in human gene

transfer trials consist of the following types: retroviral, used in approximately 60 percent of clinical trials; adenoviral, used in approximately 10 percent of clinical trials; other viral vectors, used in approximately 10 percent of clinical trials. The other 20 percent of vectors used in such trials consist of nonviral vectors.[1] The following section describes each of these systems and briefly highlights their advantages and disadvantages.

Retroviral Vectors

Retroviral vectors used in gene transfer research have been modified primarily to accomplish two goals: to infect host cells but not replicate in them, thereby preventing their spread to other cells of the body, and to accept exogenous DNA (i.e., a corrected copy of a defective gene) in lieu of their own DNA without affecting ability to infect and integrate into the host genome. Murine Moloney leukemia virus (MuLV), a retroviral vector used traditionally in gene transfer experiments, has been manipulated to accept up to 8 kb[2] of exogenous DNA. MuLV-based vectors recognize and bind to specific receptors on the target cell and subsequently internalize their nuclear material. Cells lacking this receptor are not receptive to infection by the viral particle. Although attempts have been made to modify this recognition by attaching specific ligands[3] to the surface of the viral particle such that it will recognize a particular target cell, they have been largely unsuccessful. This is because manipulation of the viral surface proteins appears to affect its ability to inject genetic material into the target cell. Retroviral vectors infect only dividing cells, and this poses a major drawback in the use of these vectors for gene therapy since it limits the types of target cells that can be used. Certain retroviruses such as lentiviruses (e.g., HIV-1) can infect nondividing cells, but their use raises issues of safety because of the possibility of recombination with endogenous cellular sequences that may result in the production of a pathogenic virus.[4] Currently, attempts are being made to create hybrid vectors that combine useful features of various retroviruses in the hope that a better vector for gene therapy may be created.

Another limitation of retroviral vectors is their inability to accommodate more than 8 kb of DNA. This size limitation usually prevents the inclusion of the exogenous gene's own regulatory elements, which may be large or have spatial requirements that cannot be accommodated by the vector. As a result, exogenous DNA expression is often driven by viral elements present in the vector (elements in the long terminal repeats, or LTRs), and this could pose a problem with correct expression of the gene. This drawback is of particular significance in germ-line interventions because of the potential to affect multiple

generations. Additionally, retroviral vectors integrate randomly in the genome, and could disrupt endogenous gene expression near the site of integration. Therefore, their use for directed germ-line manipulation may not be ideal, since altered gene expression could adversely affect embryogenesis.[5]

Adenoviral Vectors

Adenoviral vectors are derived from DNA viruses and are currently used in gene transfer trials related to, for example, cystic fibrosis and cancer treatment. These viruses are large, and vectors derived from them can accommodate up to 35 kb of exogenous DNA. Unlike retroviruses, they have the ability to infect nondividing cells. To accommodate exogenous DNA, however, several viral genes have been deleted. As a result, the engineered virus has lost its ability to control host immunogenic response. This response against the vector, combined with the inability of adenoviral vectors to integrate into the host genome, results in their loss over a period of time. In current human gene transfer trials, repeated treatments are used to combat the problem of vector loss. Since such an approach is not feasible with human germ-line interventions, the use of these vectors in their current form for such applications is limited.[6] Research on hybrid vectors combining adenovirus and retrovirus is currently being conducted, and offers the potential of overcoming the problems of each individual vector system.[7]

Other Viral Vectors

Another DNA viral vector currently used in gene transfer is the adeno-associated virus (AAV), a nonpathogenic virus that is naturally widespread in the human population. Although the original virus has the ability to integrate into the genome at a specific site, the short arm of chromosome 19, AAV vectors derived from this virus have lost this ability. These vectors also have an additional disadvantage of only accommodating a small amount of DNA. In spite of these shortcomings, AAV viral vectors have been used for infecting brain, liver, skeletal muscle, and some blood cells. Currently, researchers are trying to create hybrid vectors that would combine some of AAV's positive properties with other viruses.[8]

### *Nonviral Methods*

Direct Microinjection of DNA into Zygotes

Direct microinjection of DNA into zygotes is a technique used to create transgenic animals. It has been used widely in mice and in farm animals such as pigs, cows, and sheep.[9] The procedure involves injecting multiple copies of

DNA molecules directly into the male pronucleus of a fertilized egg via a fine needle.[10] However, the use of this technique in humans is very limited due to the following drawbacks: (1) it is a very inefficient process at present, and is not yet suitable for clinical use; (2) the microinjected DNA integrates randomly into the genome and can therefore cause insertional mutants; (3) multiple copies of the DNA are integrated into the genome, and this along with the random site of integration may affect the level of gene expression; and (4) the uptake of DNA at any stage after the one-cell stage may result in the production of a mosaic organism (i.e., an organism in which only some cells of the body carry the transgene).

### Liposome-Mediated Transfer

Liposomes are small lipid vesicles that are used as vehicles to carry drug and genes.[11] Liposome-mediated drug transfer is particularly desirous because of high drug-carrying capacity. However, liposomes have several disadvantages—these include short shelf life, inability to target specific tissues, and rapid clearance in the body. Some of these problems have been overcome by altering liposomes' surfaces so that they can target specific cells and are attacked less vigorously by the phagocytic cells[12] of the body.

Currently, drug-carrying liposomes are used for the treatment of HIV-associated Kaposi sarcoma and fungal infections in cancer, and for providing antibodies against cancerous oncogenes in breast cancers. Cationic (positively charged) liposomes offer an efficient system for delivering DNA to certain cells, since DNA (negatively charged) has a natural affinity for these vesicles. Patients with cancer and certain genetic diseases have received corrected copies of genes encapsulated in liposomes.[13] The development of liposomes as DNA carriers may prove important in the clinical use of human artificial chromosomes and synthetic oligonucleotides[14] for gene therapy.[15]

## Other Methods for Altering DNA Content in Cells

### *Human Artificial Chromosomes (HAC)*

Chromosomes are linear arrays of DNA molecules that exist in either a condensed or extended form. In nondividing cells, chromosomes exist as a delicate network of interconnected fine threads, whereas during cell division (particularly metaphase) they condense and appear as compact bodies that can be individually identified by size, shape, and banding patterns.

The basic functional elements of chromosomes include telomeres and centromeres. Telomeres are DNA-protein complexes that occur at the ends of the chromosome and serve to protect the tips from end-to-end fusion as well as prevent loss of DNA during replication. Telomeric sequences of human chromosomes are well understood. Centromeres are indented regions of chromosomes that contain tandem arrays of DNA repeats. During cell division, centromeric regions of chromosomes serve as attachment sites to protein fibers that help pull chromosomes apart. Although some progress has been made in the understanding of human centromeres, the sequence requirement for these is not yet clearly understood.

Artificial chromosomes that can be experimentally manipulated were first developed in yeast (*Saccharomyces cerevisiae*) in 1987, and are called yeast artificial chromosomes, or YACs. One of the major challenges in the manipulation of human chromosomes is their large size. Efforts to produce human artificial chromosomes have focused on creating a smaller version of the chromosome, or a "minichromosome," by using two techniques: (1) paring down an existing functional chromosome or (2) building up from minimal DNA sequences specifying the potential functional elements.[16]

Paring down has been achieved by using fragmentation vectors that contain telomeric sequences. When the vector combines with endogenous centromeric sequences, its telomeric DNA induces chromosome breakage and seeds a new telomere. Using this technique, the human Y chromosome has been pared down to a minimum length of 3.5 Mb.[17] This approach has also been successful in creating a functional artificial chromosome in mice.[18] This was done by gutting a natural chromosome of all its functional genes but retaining telomeres, centromeres, and other regions of noncoding DNA on each of the four chromosomal arms, and adding one functional marker gene, beta galatosidase, to help in tracking the chromosome through generations. Mice containing this artificial chromosome not only expressed the foreign gene, but also transmitted it to three generations of descendants without any harm to the animals.

Building up from minimal sequences requires combining all the putative functional elements into vectors such as YACs and introducing them into cells. This technique has limited uses currently, as the minimal sequence requirements for HAC are not well understood. Harrington et al. (1997)[19] described a method that introduced human telomeric and putative centromeric DNA sequences along with genomic DNA into cells, and analyzed stable clones for the

presence of minichromosomes. Using this method, nine minichromosomes were generated. Using a cell to assemble a minichromosome in the presence of genomic DNA and certain minimal functional elements could represent a way to better identify and characterize the unknown functional elements of human artificial chromosomes. Development of better technologies for efficient ways of creating, introducing, and manipulating human artificial chromosomes are necessary before this technique can be clinically applicable.

## Repair Mechanisms

### *Homologous Recombination*

Homologous recombination techniques are the oldest method by which in vivo DNA repair has been achieved. As the name suggests, introduced foreign DNA replaces the endogenous DNA in cells by recombining with the endogenous sequences. In mice, homologous recombination has been used for gene replacement by replacing the endogenous gene with an introduced stretch of DNA.[20] This is described in greater detail below on the use of embryonic stem cells.

### *RNA/DNA Hybrid Oligonucleotides*

The use of chimeric RNA/DNA hybrid oligonucleotides to cure single-base mutations in genes is a particularly promising method of achieving corrections. Initial in vitro experiments with RNA/DNA hybrids indicate that they are effective in promoting homologous pairing reactions both in episomal[21] DNA and in genomic DNA in cultured replicating cell lines.[22] To date, effective in vivo site-directed mutagenesis using this technique has been achieved both in isolated primary liver cells (they are quiescent and nonreplicating) and in intact livers of rats by using RNA/DNA hybrid oligonucleotides.[23] The oligonucleotide's sequence, complementary to the target gene except for a single mismatched nucleotide, corrects the defect when aligned with the complementary genomic DNA sequence. The exact mechanism by which this correction is mediated is unknown. The rate of nucleotide exchange varied both in isolated cells and in intact liver, although in both cases it was dependent on the amount of vector used. In isolated cells, a maximum efficiency of 19 percent was reported, while in intact liver the maximum efficiency was 40 percent. In addition to several advantages over traditional viral vectors, such as lack of random integration of DNA and immunogenicity[24] of viral proteins, this gene

conversion method offers an additional advantage: the expression of the altered gene is controlled in vivo by its own regulatory elements. Currently, one of the major drawbacks to the clinical use of this technique is the lack of efficient delivery mechanisms to particular tissues.

### *Triple Helix-Forming Oligonucleotides*

Bifunctional oligonucleotides that form triplex DNA structures in cells have been successfully applied to human cells resulting in correction of mutations in 1 to 2 percent of cells.[25] The primary disadvantage of this method is that the target DNA must contain continuous stretches of purines[26] and pyrimidines,[27] thereby limiting the number of genes that can be targeted. While gene repair strategies hold great promise for gene therapy, there needs to be substantial research of such techniques in human model systems and clinical trials before they would be appropriate for germ-line intervention.

## Cells That Could Facilitate Germ-Line Interventions

Cells that could potentially facilitate human germ-line interventions fall into two categories: (1) embryonic stem (ES) and embryonic germ (EG) cells, pluripotent cells that could give rise to a number of tissues, including germ-line cells; and (2) spermatogonial stem cells, precursors of sperm. Both categories of cells have the defining features of stem cells (i.e., the ability to self-renew and to differentiate into more specialized cells). Although stem cells have been isolated from animals, recent reports describe the isolation and characterization of human ES and EG cells. Each of these findings and their implications are briefly discussed below.

### *Embryonic Stem and Germ Cells*

ES and EG cells are isolated from an early stage of embryonic development called the blastocyst,[28] while EG cells are isolated from the genital ridge[29] of early embryos. A distinct characteristic of these cells is that they have the capacity to proliferate indefinitely in an undifferentiated stage in vitro, while they can be introduced in vivo and give rise to cell types of all three germ layers, namely, ectoderm,[30] mesoderm,[31] and endoderm.[32] Both types of cells were isolated initially from mouse embryos and have been used in mice for producing chimeras. Chimeras derived from ES cells have been studied extensively to give rise to homozygous[33] animals derived only from these cells, demonstrat-

ing their potential to contribute to the germ-line lineage. Studies on EG cell-derived chimeras, on the other hand, have been limited. Although some studies have demonstrated their potential to contribute to the germ-line lineage, recent findings indicate that such chimeras have size and skeletal abnormalities.[34] ES and EG cells have been isolated from a number of species, including humans.[35] The pluripotency[36] of human ES cells in vivo was demonstrated by implanting them in mice, while the pluripotency of human EG cells was shown by analyzing embryoid bodies formed in vitro. Both these studies revealed the presence of cell types from all three germ layers. However, the ultimate test of their pluripotency (i.e., contribution to germ cells) can be done only by creating chimeras,[37] which has currently not been undertaken with human ES cells. Mouse ES cells have been used to modify the germ line genetically in specific ways. The current inefficiency of this procedure precludes its use with humans. However, studies on human ES cells, particularly in the role of genes in early embryonic development, may lead to findings that could facilitate human germline interventions.

Although technically roundabout, human ES cells derived from fertilized eggs could be manipulated in vitro, and nuclei from resultant cells could be transferred to enucleated eggs via somatic cell nuclear transfer (cloning) and reimplanted to develop into individuals. Manipulations of ES cells in vitro, particularly with the intent of altering the germ line in a directed and controlled manner, has been done extensively in mice. This process, called gene targeting, is mediated via the process of homologous recombination, where parts of the endogenous[38] gene are replaced with an introduced stretch of DNA.[39] In mice, altered ES cells are returned to the early embryo to generate chimeric mice (i.e., made up of a mixture of cells from two different animals), which are bred again to transmit the altered genes to the next generation.[40] Until the isolation of human ES cells, gene targeting via homologous recombination was not possible in humans. However, the availability of these cells along with the advent of new technologies such as cloning make it a possibility in humans.

### *Spermatogonial Stem Cells*

Spermatogonial stem cells have the ability to divide and generate two different types of cells: more stem cells and cells capable of entering the differentiation pathway to form mature sperm. The regenerative nature of these cells offers the potential to provide an inexhaustible supply of cells. There have

been two major accomplishments in this field. Mouse stem cells have been cryopreserved, thawed, and reimplanted successfully into mice, and rat stem cells have been transplanted in mice.[41] Both these methods resulted in the production of normal mature sperm, although the ability of these sperm to fertilize eggs is yet untested. While such studies have not been reported in humans, these techniques hold promise for human germ-line intervention. Stem cells could be isolated from humans, grown, manipulated, and implanted back into either humans or perhaps mice to yield mature sperm. If efficient methods for gene introduction and expression become available, the development of such spermatogonial stem cell technology would facilitate germ-line interventions.

## Other Methodologies Pertinent to Inheritable Changes in Human DNA

The methodologies described below depend on nuclear transfer, distinguishable by the type of cell a nucleus is derived from, namely, egg, embryo cell, or somatic cell. Egg cell nuclear transfer involves removing the nucleus from an egg cell, placing it in the intact cytoplasm of an enucleated egg, and allowing this hybrid egg to be fertilized in vitro before implantation. Embryo cell nuclear transfer, a technique used in animals, requires separating a four- to eight-cell embryo into separate cells (blastomeres), removing the nucleus from one cell, and transferring it to an enucleated donor egg. Somatic cell nuclear transfer involves the removal of a nucleus from an adult cell, followed by its placement into an enucleated egg cell and then allowing development to proceed.[42]

### *Correcting Mitochondrial Defects*

Mitochondria are subcellular structures that number from hundreds to several thousands within each cell, have their own DNA, and replicate separately from nuclear DNA. In contrast to 50,000 to 100,000 genes contained in the nuclear DNA, mitochondrial DNA contains only thirty-seven genes. Mitochondria are inherited maternally and found in the cytoplasm of the egg; no mitochondria are contributed by sperm during fertilization. A number of inherited disorders are mitochondrial in origin,[43] and for such patients germ-line gene therapy may be an option in ensuring that the disease is not passed on to

offspring. Such germ-line therapy may be accomplished by egg cell nuclear transfer or in vitro nuclear transplantation (IVONT). This would result in the production of a hybrid egg, where the nuclear DNA of one woman would be mixed with the mitochondrial DNA of another woman. Although a number of safety concerns, such as compatibility, immunogenic response, and effectiveness if some of the original mitochondrial DNA remained, have been raised, a technique involving injection of cytoplasmic material, containing mitochondria, from the egg of one woman to the egg of another has resulted in the birth of nearly thirty children so far. Analysis of mitochondrial DNA from some of the resulting children has shown that they contain donor mitochondria, thus demonstrating clearly that human germ-line genetic modification had occurred.[44]

### *Cloning*

In its most basic definition, cloning refers to a precise copy of a molecule, cell, plant, animal, or human being. In its current popular meaning, cloning refers to the process of transferring a nucleus from an adult cell to an enucleated egg cell and allowing it to develop into a whole organism. The process of transplanting an adult nucleus into an enucleated egg cell and allowing it to grow into an organism was achieved in vertebrate animals, initially in frogs, in 1975.[45] However, those experiments in frogs only generated tadpoles and not adult frogs. Successful cloning from adult cells, leading to the formation of a fully developed animal, was achieved for the first time in mammals with the cloning of Dolly.[46] It has since been reported for other mammalian species as well, including cows and mice.[47] Human cloning is technically feasible and appears to have been attempted.[48] The technique of cloning could facilitate human germ-line gene interventions. For example, nuclei from genetically altered isolated cells could be transplanted into enucleated eggs and reimplanted into the uterus and allowed to develop into a fetus.

Human inheritable genetic modifications have already occurred inadvertently as a result of treating infertility. These genetic modifications, however, were not in nuclear DNA, which contains most of the genetic information, nor did they use recombinant DNA technologies. However, rapid scientific advancements in the coming decade are likely to make deliberate human inheritable genetic modifications feasible. As a society, we need to get ready for the very real possibility that scientists will break another genetic barrier, one that will reverberate through generations to come.

NOTES

1. W. French Anderson, "Human Gene Therapy," *Nature (supplement)* 392 (1998): 25–30.

2. $1 \times 10^3$ base pairs.

3. An extracellular molecule that recognizes and attaches to a "receptor," usually a target protein on the surface of a cell. Following attachment, the substance enters the cell.

4. Rafael G. Amado and Irvin S. Y. Chen, "Lentiviral Vectors: The Promise of Gene Therapy within Reach?" *Science* 185 (1999): 674–76.

5. The development of an individual from a fertilized ovum; the process of embryo formation.

6. Anderson, "Human Gene Therapy," 25–30.

7. Chen Zheng, Buzz J. Baum, Michael J. Iadarola, and Brian C. O'Connell, "Genomic Integration and Gene Expression by a Modified Adenoviral Vector," *Nature Biotechnology* 18 (2000): 176–80.

8. Anderson, "Human Gene Therapy," 25–30.

9. Jon W. Gordon, "Transgenic Animal," *International Review of Cytology* 115 (1989): 171–229; and Kevin A. Ward and Collin Nancarrow, "The Commercial and Agricultural Applications of Animal Transgenesis," *Molecular Biotechnology* 4 (1995): 167–78.

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11. Robert Langer, "Drug Delivery and Targeting," *Nature (supplement)* 392 (1998): 5–10.

12. A specialized cell, such as a macrophage, which ingests and usually destroys foreign particulate matter or microorganisms.

13. Kaarin K. Goncz, Karl Kunzelmann, Zhi Xu, and Dieter C. Gruehert, "Targeted Replacement of Normal and Mutant CFTR Sequences in Human Airway Epithelial Cells Using DNA Fragments," *Human Molecular Genetics* 7 (1998): 1913–19.

14. The partial hydrolysis/synthesis product of nucleic acids, consisting of a few nucleoside phosphate residues joined together.

15. Langer, "Drug Delivery and Targeting," 5–10.

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17. Huntington F. Willard, "Chromosome Manipulation: A Systematic Approach toward Understanding Human Chromosome Structure and Function," *Proceedings of the National Academy of Sciences USA* 93 (1996): 6847–50.

18. Deborah O. Co, Anita H. Borowshi, Josephine D. Leung, Jos van der Kaa, Sandra Hengst, Gerald J. Platenburg, Frank R. Pieper, Carl F. Perez, Frank R. Jirkin, and Jan I. Drayeer, "Generation of Transgenic Mice and Germline Transmission of a Mammalian Artificial Chromosome Introduced into Embryos by Pronuclear Microinjection," *Chromosome Research* 15 (2000): 345–55.

19. John J. Harrington, Gil Van Bokkelen, Robert W. Mays, Karen Gutshaw, and Huntington F. Willard, "Formation of de Novo Centromeres and Construction of First-Generation Human Artificial Microchromosomes," *Nature Genetics* 15 (1997): 345–55.

20. Mario R. Capecchi, "The New Mouse Genetics: Altering the Mouse Genome," *Trends in Genetics* 5 (1989): 70–76.

21. An independent extrachromosomal DNA molecule is referred to as an episome.

22. Kyonggeun Yoon, Allyson Cole-Strauss, and Eric B. Kmiec, "Targeted Gene Correction of Eposomal DNA in Mammalian Cells Mediated by a Chimeric RNA/DNA Oligonucleotide," *Proceedings of the National Academy of Sciences USA* 93 (1996): 2071–76; and Allyson Cole-Strauss, Kyonggeun Yoon, Yufei Xiang, Bruce C. Byrne, Michael C. Rice, Jeff Gryn, William K. Holloman, and Eric B. Kmiec, "Correction of the Mutation Responsible for Sickle Cell Anemia by an RNA-DNA Oligonucleotide," *Science* 273 (1996): 1386–89.

23. Betsy T. Kren, Paramita Bandhopadhyay, and Clifford J. Steer, "In Vivo Site-Directed Mutagenesis of the Factor IX Gene by Chimeric RNA/DNA Oligonucleotides," *Nature Medicine* 4 (1998): 285–90.

24. The quality that makes a substance immunogenic (capable of evoking an immune response), or the degree to which a substance possesses this quality.

25. Gan Wang, Dan D. Levy, Michael D. Seidman, and Peter M. Glazer, "Targeted Mutagenesis in Mammalian Cells Mediated by Intracellular Triple Helix Formation," *Molecular Cellular Biology* 15 (1995): 1759–68.

26. The larger of two types of nucleotide bases found in DNA and RNA; includes adenine (A) and guanine (G).

27. The smaller of two types of nucleotide bases found in DNA and RNA; includes cytosine (C), thymine (T), and in RNA only uracil (U).

28. The modified blastula stage of mammalian embryos, made up of the inner cell mass and a thin layer of cells that encloses it.

29. An area of thickened cells on the ventromedial border of the embryo that develop into the testes or ovaries.

30. The outermost layer of the three primary germ layers of an early embryo.

31. The middle of the three primary germ layers of an early embryo.

32. The innermost of the three primary germ layers of an early embryo.

33. Having identical rather than different alleles at a given locus on both homologous chromosomes.

34. Patricia A. Labosky, Denise P. Barlow, and Brigid L. M. Hogan, "Mouse Embryonic Germ (EG) Cell Lines: Transmission through the Germ Line and Differences in the Methylation Imprint of Insulin-Like Growth Factor 2 Receptor (Igf2r) Gene Compared with Embryonic Stem (ES) Cell Lines," *Development* 120 (1994): 3197–3204; Colin L. Stewart, Inder Gadi, and Harshida Bhatt, "Stem Cells from Primordial Germ Cells Can Reenter the Germ Line," *Developmental Biology* 161 (1994): 626–28; Sabine Steghaus-Kovac, "Ethical Loophole Closing Up for Stem Cell Researchers," *Science* 286 (1999): 31.

35. Antonio Regalado, "The Troubled Hunt for the Ultimate Cell," *Technology Review* (July/August 1998): 34–41; James A. Thomson, Joseph Itskovitz-Eldor, Sander S. Shapiro, Michelle A. Waknitz, Jennifer J. Swiergel, Vivienne S. Marshall, and Jeffrey M. Jones, "Embryonic Stem Cell Lines Derived from Human Blastocysts," *Science* 282 (1998): 1145–47; Michael J. Shamblott, Joyce Axelman, Shunping Wang, Elizabeth M. Bugg, John W. Littlefield, Peter J. Donovan, Paul D. Blumenthal, George R. Huggins, and John D. Gearhart, "Derivation of Pluripotent Stem Cells from Cultured Human

Primordial Germ Cells," *Proceedings of the National Academy of Sciences USA* 95 (1998): 13726–31.

36. The ability to give rise to cells of all three germ layers, ectoderm, mesoderm, and endoderm, thereby forming the body organs, nervous system, skin, muscle, and skeleton.

37. An organism consisting of two or more genetically distinct cell types.

38. Originating, developing, or growing from within.

39. Capecchi, "The New Mouse Genetics," 70–76.

40. Elizabeth J. Robertson, "Pluripotential Stem Cell Lines as a Route into the Mouse Germ Line," *Trends in Genetics* 2 (1986): 9–13.

41. Mary R. Avarbock, Clayton J. Brinster, and Ralph L. Brinster, "Reconstitution of Spermatogenesis from Frozen Spermatogonial Stem Cells," *Nature Medicine* 2 (1996): 693–96; and David E. Cloutheir, Mary R. Avarbock, Shanna D. Maika, Robert E. Hammer, and Ralph L. Brinster, "Rat Spermatogenesis in Mouse Testis following Spermatogonial Stem Cell Transplantation," *Nature* 381 (1996): 418–21.

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43. Donald S. Rubenstein, David C. Thomasma, Eric A. Schon, and Michael J. Zinaman, "Germ-Line Therapy to Cure Mitochondrial Disease: Protocol and Ethics of In Vitro Ovum Nuclear Transplantation," *Cambridge Quarterly of Healthcare Ethics* 4 (1995): 316–39.

44. Jacques Cohen, Richard Scott, Tim Schimmel, Jacob Levron, and Steen Willadsen, "Birth of Infant after Transfer of Anucleate Donor Oocyte Cytoplasm into Recipient Eggs," *The Lancet* 350 (1997): 186–87; Jacques Cohen, Richard Scott, Mina Alikani, Tim Schimmel, Santiago Munne, Jacob Levron, Liza Wu, Carol A. Brenner, Carol M. Warner, and Steen Willadsen, "Ooplasmic Transfer in Mature Human Oocytes," *Molecular Human Reproduction* 4 (1998): 269–80; J. A. Barritt, Carol A. Brenner, H. E. Malter, and Jacques Cohen, "Mitochondria in Human Offspring Derived from Ooplasmic Transplantation," *Human Reproduction* 16 (2001): 513–16.

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46. Ian Wilmut, Angelika E. Schnieke, Jim McWhir, Alexander J. Kind, and Keith H. S. Campbell, "Viable Offspring Derived from Fetal and Adult Mammalian Cells," *Nature* 385 (1997): 810–13.

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48. Rick Weiss, "Cloned Human Embryos Created, South Korean Researchers Say," *Washington Post,* December 17, 1998, A3; and Rick Weiss, "Embryo Work Raises Specter of Human Harvesting, Medical Research Teams Draw Closer to Cloning," *Washington Post,* June 14, 1999, A1.

CHAPTER FIVE

# Germ-Line Modification in Clinical Medicine

## Is There a Case for Intentional or Unintended Germ-Line Changes?

R. Michael Blaese, M.D.

During the past decade, a number of technical advances have reignited the need for thoughtful consideration of the issues surrounding human germ-line modification. The unexpectedly rapid progress by the Human Genome Project has put the sequence of the entire human genome within our grasp.[1] Further, improvement in the techniques for somatic cell gene therapy[2] has led inevitably to discussions of the use of this approach to treat fatal genetic conditions during intrauterine fetal life.[3] In this chapter I discuss some of the technical issues facing the potential intentional application of germ-line gene modification and provide a contextual framework for discussion of the implications of germ-line changes that may occur as an unintended consequence of medical therapy.

## Proposed Clinical Indications for Germ-Line Modification

From the perspective of potential clients requesting germ-line modification (GLM), what might they want to accomplish by using this technology? The obvious answer is to predetermine part of the genetic inheritance of their offspring. Most frequently this question is raised by potential parents who wish

to produce offspring free of a particular genetic disease for which their carrier status has been confirmed. It is easy to sympathize with the desire of the parents of a child suffering from a serious genetically based deformity or disease that they not pass this same disorder along to additional children. Disorders most frequently cited as candidates for germ-line intervention are those affecting multiple body systems (e.g., cystic fibrosis) or those disorders that are widely distributed in the body (e.g., Duchenne muscular dystrophy). In addition, genetic disorders that lead to fetal death (e.g., alpha thalassemia) or lead to defects that are irreversible by the time of birth (e.g., anencephaly) would be potential candidates for this type of treatment. The issues become much more difficult when the genetic modification proposed does not involve prevention of an obviously serious medical disorder but rather would enhance physical characteristics, intelligence, or other traits that the potential parents might find desirable. Several of the other contributions to this volume discuss in detail the issues of genetic enhancement and the definition of disease. The arguments in this chapter are restricted to the use of these technologies for the treatment of lethal or seriously disabling diseases that cannot be effectively treated by traditional medical therapy.

## Reproductive Options Available to Carriers of Serious Genetic Disease

What options are currently available for carriers of serious genetic mutations wishing to avoid having a child suffering from an inherited disease? One obvious option is for the couple not to conceive additional children. If they are determined to have additional children, there have been two options available. One involved genetic testing of the fetus followed by selective termination of the pregnancy if the fetus was found to have the disorder in question. The second more recently available option involves IVF (in vitro fertilization) with preimplantation genetic diagnosis performed on early eight-cell embryos and then selective implantation of an unaffected embryo.[4] A third option has recently been proposed that would use the techniques of somatic cell gene therapy to treat an affected fetus in utero to correct the genetic disorder before fatal or irreversible defects develop.[5] This type of intervention might carry with it the possibility for introducing the same genetic modification into the developing reproductive tissues of the treated fetus and thus unintentionally modify the germ line.

Another proposal would be to somehow treat the potential parents to modify their reproductive tissues (in vitro or in vivo) so that their sperm or ova would not contain the disease-causing gene of concern. This would be GLM at its most basic level and would be the only way for a couple to parent disease-free offspring in the improbable scenario that both prospective parents were homozygous for a disease-causing recessive gene or when one was homozygous for a dominant disease-causing gene. Although this theoretical scenario has often been raised, if such gene carriers had reached the age when they were seriously contemplating having children and were sufficiently healthy to rear them, their gene disorder is unlikely to be severe enough to qualify for germ-line intervention.

## Consumer Expectations

What about this type of treatment for potential parents who are asymptomatic heterozygous carriers for a serious recessive genetic disorder—the most common situation faced by couples wishing to have additional children following the birth of one child affected by a serious genetic disease? To help answer this question, it is useful to consider it from the perspective of consumers and their expectations. Medical consumers have come to expect that procedures and products used in their care have been tested to meet certain "safety" criteria. This safety concern holds for both treated individuals and, especially in the case of germ-line products, their offspring and the generations to follow. The relative safety of medical products used in the United States is regulated by the Food and Drug Administration (FDA) and is usually evaluated in preclinical animal models followed by an extensive series of clinical trials. What level of risk is acceptable and how will it be evaluated? Another critical concern of consumers is the efficacy of the treatment. If one were to undergo a complex and expensive procedure to prevent the transmission of a lethal genetic disorder to his or her offspring, anything less than 100 percent efficacy of the procedure would seem to be unacceptable. If there were still the chance of having a genetically disabled child following the procedure, then another technique that could give higher assurance of success would become the technique of choice.

Given these consumer expectations, it is very difficult to envision a process that would allow the technology of intentional GLM to develop through the traditional clinical trial route. While males produce millions of sperm daily for

most of their adult lives, human females have a fixed number of ova that are already present in their ovaries at birth. The technical challenge of achieving complete and accurate genetic modification of all sperm or all ova in a potential parent seems very remote, even in the most optimistic of scenarios. The reproductive systems of most experimental animals are sufficiently different from those of man that preclinical animal testing of candidate gene modification technologies may not be informative for the human situation. Further, many of the usual criteria under which such clinical trials are evaluated would not be present. Is a traditional risk/benefit analysis possible when the treatment is given to an asymptomatic carrier to affect the outcome or incidence of a disease in a future generation? What is the appropriate mechanism for obtaining "informed consent"? From future generations? How could efficacy be tested without putting the parents and future generations at significant risk of continued transmission of the unwanted genetic disorder? How many generations would need to be evaluated to determine the overall safety of the procedure? Although not without its own set of issues, IVF combined with preimplantation genetic diagnosis and selective implantation of an unaffected embryo would appear to allow carrier-parents to conceive a child free of the genetic disorder in question, while also providing a much higher level of certainty of success than some yet-to-be-developed procedure for correcting the genetics of their germ cells.

## Technological Constraints

The technology used to date in somatic cell "addition" gene therapy trials would be inappropriate for intentional germ-line modification for several reasons. With current technology, a normal copy of the gene in question is inserted into a vector that is then used to carry the transgene into the genome of the host cell to substitute for the function of the defective gene. These vectors are derived from modified viruses or other microorganisms and insert, in addition to the human gene, genetic sequences that are derived from the parent vector plasmid or virus. Further, since most vectors that permit integration of the transgene into the chromosomes of the targeted host cell have limited capacity, shortened genes or cDNAs (complementary DNAs) are usually employed. cDNA, although containing the sequence of the coding region of the gene, has had critically important regulatory information contained in the genomic promoter and introns deleted, as well as containing only one of the sometimes sev-

eral potential splice variants of the original gene. Thus, physiologic regulation of the gene cannot be achieved with cDNA transgenes. Furthermore, gene addition will not be corrective if a dominant mutation is causing the disease (e.g., Huntington's disease) or if the mutant gene causes the production of a pathologic gene product (e.g., sickle cell anemia).

Every integrating vector system so far developed provides for only random integration of the transgene somewhere in the host chromosomal DNA. Each integration event will occur in a different location so that the activity of the transgene from one cell to the next will vary, depending on the local geography of vector integration site in that cell. Some integrants will express at high levels, while others may not express at all. When used in somatic gene therapy of a population of cells, this wide range in gene expression from cell to cell averages out across the population of treated cells. However, at the level of single stem cells or single germ cells, with widely varying transgene expression depending on the position of the random vector integration, all the cells of each resulting individual will be genetically identical and therefore the whole tissue or individual may unpredictably overexpress the transgene or maybe not express it at all. Further, with the use of these "addition" gene therapy vectors, the original defective gene remains unmodified in the patient's genome. Since the transgene that is providing a replacement for the original gene's defective function is randomly integrated on any chromosome (forty-six choices) of the target cell, it is not likely to be physically located on or linked to the chromosomal location of the endogenous defective gene. With a single copy of the "corrective gene" located at a separate chromosomal location from the disease-causing gene, during chromosomal separation and rearrangement at meiosis the "disease-causing" and "disease-correcting" genes will separate. As a normal consequence, in 50 percent of the resulting gametes the "correction" will be lost to the next generation.

Given the inherent limitations of "addition" gene therapy, is there any process that might be used for this GLM? One process that does match the needs of germ-line modification for correction of a genetic defect is homologous recombination. In this process, a normally "spelled" gene segment is swapped for the segment with the defect. Unfortunately, homologous recombination is very inefficient and also has a significant incidence of random insertion in addition to the specific recombination that is desired. Studies of the natural processes by which the DNA sequence is proofread and corrected during normal cell division have given insights into other potential mechanisms

for repairing mutant genetic sequences. These mechanisms fall under the general term *gene repair,* and their application to gene therapy has shown significant promise in early preclinical models testing their ability to correct genetic defects leading to disease in animals.[6] In this class of technology, a correctly spelled fragment of DNA ranging in length from forty to a thousand bases is introduced into living cells, and in the cell's nucleus it appears to be used as a template that, in conjunction with the cell's own DNA repair machinery, permanently changes and corrects the mutant genomic DNA sequence. This technology does not add any foreign DNA into the genome, is highly specific so that only the coding sequence of the mutant gene is corrected, and permits normal physiologic regulation of the corrected gene's expression. Since this process corrects the defective gene itself rather than randomly adding an additional normally spelled copy of the gene, all of the germ-line progeny of the corrected cell will be corrected and the disease will be eradicated from future generations. At this time it appears that if germ-line intervention will eventually be considered for prevention of genetic diseases, some form of gene repair strategy is the most likely technology to be employed.

## Germ-Line Modification as an Unintended Consequence of Somatic Gene Therapy

As mentioned earlier, one of the strategies for treating genetic disorders that are characterized by wide distribution in the body or by defects that are lethal to the fetus or irreversible by the time of birth is to apply the techniques of somatic cell gene therapy to the embryo or developing fetus. In my view, this and other forms of somatic gene therapy represent a fundamentally different situation from that encountered in the scenarios for potential germ-line intervention, where the reproductive tissues of the prospective parents are intentionally genetically modified. In this case we are proposing true therapy of the diseased individual herself or himself and are not entering into the treatment with the goal of affecting future generations. The potential for germ-line modification in this situation stems from either the very early stage or the systemic nature of the treatment so that genetic changes introduced into the embryo or fetus to correct its disease might also have a chance to modify cells that will eventually develop into the reproductive tissue of the individual—a secondary consequence of the treatment of disease.

As an important point of context relating to the potential of somatic cell gene

therapy resulting in germ-line modifications, routine medical practice is not prevented from employing a wide range of treatments for diseased patients just because those treatments may affect the germ line. The most common examples are found in the therapy of life-threatening cancer, where many of the most effective treatments are also known to be capable of inducing mutations in the normal cells (including potentially the germ cells) of the treated individuals. Cancer therapy is not withheld from individuals in their childbearing years or otherwise restricted in its use for fear that it may affect the germ line and thus future generations. Radiation therapy can also readily induce mutations, as can even routine diagnostic X-rays and environmental exposure to sunlight and natural mutagenic agents. What is held as the primary concern in these cases is the risk/benefit ratio of the treatment for the individual with the disease in question. Thalidomide provides an informative example of how this risk/benefit analysis has been employed in practice. When given as a sleeping aid to pregnant women, thalidomide was found to cause profound skeletal defects in their unborn fetuses and its use was banned. However, two decades later the same agent was shown to be useful in the therapy of cancer and serious immune disorders and its use for those indications was permitted. Sleeping aid = no, cancer therapy = yes. If given a choice of treatments, selection of those treatments most highly effective in the patient's disease are given preference even if they might have a greater intrinsic mutagenicity because, since the time of Hippocrates, society has held that a physician's primary obligation is to the patient.

What is the germ-line risk from our attempts at somatic gene therapy in postnatal life? With the current technology these seem to be very small. Most integrating gene transfer systems in current use (e.g., murine retroviruses) are able to integrate their genes only in cells that are replicating their DNA and dividing. Therefore, germ-line modification of the ova would be very unlikely since a woman's ova are not dividing and are already developed by the time of birth. The sperm-generating cells are actively dividing, but the unique vascular supply of the testis appears to protect the sperm-producing cells from ready access by outside factors. Attempts to deliver genes intentionally to the sperm in experimental animals via the intravascular route have been completely unsuccessful.[7]

## How Stable Is the Human Genome, Anyway?

One of the unique features of the human genome as revealed by the sequencing effort of the Human Genome Project is that less than 2 percent of the

3 billion bases in our genome encodes the genes.[8] It is estimated that about 50 percent of the human genome is actually made up of genetic elements that originated from other, nonhuman sources. One type of this extra genetic material is made up of genetic sequences associated with movable genetic elements that are capable of duplication and movement from place to place within the genome. A recent analysis of the frequency of new genetic mutations[9] in a series of human disease genes estimates that one of every eight human sperm (and thus one out of eight of our fellow human beings) carries a new random insertional mutation that was caused by the jumping of one of these transposable genetic elements to a new location in the genome. The unexpected presence of this very high "background" of random insertional mutation events occurring in the human genome has caused the reevaluation of the potential influence of similar random insertional events related to our attempts at somatic cell gene therapy. With all gene addition forms of somatic cell gene therapy, the introduced transgene integrates randomly into the chromosomes of the target cell and thus has the opportunity to disrupt (mutate) another gene if it happens, by chance, to integrate at a site occupied by an endogenous gene. It was recognized that regulating the number of potential mutations in sperm related to vector administration needed to be determined in the light of the spontaneous or natural frequency of such mutations. Maintaining the frequency of permissible vector insertions to less than one in 100,000 sperm as originally proposed made very little sense in the face of a spontaneous transposition insertion rate (and thus germ-line mutation rate) of one in every eight sperm.

## Conclusion

Analysis of the potential uses of intentional germ-line modification has revealed scanty indication for developing or employing this procedure, particularly in view of the extreme technical challenges to success in this area and in comparison with the alternatives available to achieve the same goals. It is to be hoped that a mechanism can be found that will permit the careful, long-term observation of recipients of somatic cell gene therapies to help determine if unintended germ-line changes have occurred, and if so, their consequences. By contrast with the limited outlook for intentional germ-line modification, somatic gene therapy has a very promising future as a treatment for a host of genetic and acquired disorders. Prudence and caution are certainly warranted as

we progress along the path of development of these new forms of gene-based treatments. Nevertheless, overzealous implementation of restrictions on the development of somatic gene therapy based on the fear that unintentional germ-line modification may occur will seriously limit progress toward fulfilling the promise of somatic gene therapy, probably without achieving meaningful "protection of the genome" in view of the already high existing frequency of spontaneous insertional mutations. It is time for somatic gene therapy to be viewed in the same light as traditional forms of medical therapy that are directed at the treatment of serious disease.

NOTES

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5. Zanjani and Anderson, "Prospects for *in Utero* Human Gene Therapy."

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CHAPTER SIX

# Gene Repair, Genomics, and Human Germ-Line Modification

Kenneth W. Culver, M.D.

The initiation of numerous human somatic cell gene therapy experiments, the identification of scores of human genes, the recent growth of human stem cells, and progress in animal germ-line modification—all point to the likelihood of an eventual attempt at germ-line modification in humans. Under what circumstances would the accumulation of scientific information support intentional human inheritable genetic modifications (IGM)? While these recent technological advances have forced increased discussion of this question, it is precisely the knowledge gained from these technologies that will provide the basis to proceed with human IGM. The purpose of this chapter is to review key technologies that will support the initiation of human IGM and to propose a paradigm for building a foundation of confidence that IGM in humans will be successful.

## Major Scientific Obstacles to Human IGM Application

Traditionally, there have been two major unresolved scientific safety questions in the realm of IGM technology. First, would the gene transfer methods

mutate or perturb the genome, resulting in undesired inheritable consequences? This issue is particularly important for gene transfer because in this process viral and nonviral vectors are adding DNA to the genome to achieve permanent correction. A further complication is the fact that the addition of this extra DNA in the genome may occur randomly, potentially affecting other genes. The second question is, could scientists know enough about the functions of genes before these manipulations to be certain that successful correction of the gene would not have associated though unintended detrimental genetic effects? With more than 3 billion nucleotides in the human genome, the alteration of one can result in effects ranging from no consequences to severe, life-threatening effects. Therefore, a detailed understanding of the effects of any IGM procedure on the genome is essential. Satisfactory resolution of these key scientific issues must be achieved before intentional IGM is attempted in the human germ line. Reaching this level of scientific sophistication and understanding will unquestionably require the development of new, improved technologies beyond gene transfer concurrent with open public discussion. The goal of this chapter is to outline two important advances, gene repair and genomic technologies, which have moved scientific capability substantially forward, each having the potential to address one of the two major concerns adequately.

## A Paradigm for Proceeding with Intentional Human IGM

With our present understanding of the genetic basis of disease in the context of our current technological capabilities, it is possible to construct a process by which the two major scientific obstacles to human IGM can be resolved, thereby allowing for initiation of intentional IGM in humans. This process would consist of three requisite aspects: technological advances and considerations, preclinical studies/safety assessments, and the selection of disorders for initial clinical application.

Continuing technological advances are arguably the primary driving forces behind constant progress in improving the quality of clinical medicine. Therefore, it is not surprising that recent scientific progress in gene therapy research, notably new possibilities for gene repair, may reduce scientific barriers to human germ-line intervention. These new oligonucleotide-based technologies differ from traditional gene therapy (i.e., gene transfer) in that they "repair" the mutation instead of trying to compensate for lost gene function. No extra DNA

is expected to remain permanently in the cell beyond what is considered to be the "nonmutant" or "normal" sequence.

Another advantage of the gene repair approach over gene transfer is related to the need to control gene function. If one transfers a new copy of a gene into a cell (gene transfer), it typically must be accompanied by another gene to regulate its function. However, in the case of mutation correction, the regulation of gene function is maintained by genes already present in the cell and is not dependent on newly inserted genetic material. Therefore, the newly emerging field of mutation correction, or "gene repair," with its improved benefit and safety aspects holds promise for treatment of inherited disorders due to specific, limited mutations. Since most disease-causing mutations are point mutations (i.e., only one chemical base is altered), gene repair technologies have the potential for very wide applicability for both somatic and germ cell manipulation.

In the context of human IGM applications, the development of gene repair methods that do not require viral vectors is significant and should be emphasized. Germ-line intervention is distinctly different in its risk/benefit ratio compared to somatic cell genetic manipulation and therefore should be held to a higher standard. Germ-line gene therapy should be at least as safe as other options for germ-line intervention, such as in vitro ovum nuclear transfer (IVONT) or somatic cell nuclear transfer (SCNT), and meet the stringent guidelines associated with somatic cell gene therapy. IVONT and SCNT both involve the exchange of one nucleus for another. SCNT has been successfully used to clone sheep, mice, and goats, for example.[1] These procedures do not alter the DNA sequence in the target cell as do gene transfer or gene repair technologies, yet would provide correction of the mutation being treated. If IVONT and SCNT can be achieved safely, then why should a gene transfer vector be used that is expected to carry a much greater risk of adverse outcome? Viral gene transfer and viral gene repair methods have an unacceptably high risk compared to IVONT due to the transient or permanent addition of active genes into the treated cell, and therefore pose a safety hazard too great for use in the human germ line.[2]

To optimize the safety profile of gene therapy for IGM applications, nonviral gene transfer and nonviral gene repair methods should lack the insertion of active genetic elements. In addition, the most favorable approach would be the avoidance of methods that add DNA to the cell beyond restoring the normal sequence, with the goal being a final sequence that is identical to the "normal"

sequence. For example, third-strand-forming bifunctional oligonucleotides (TFBOs) have been successfully used to repair point mutations in human cells, restoring normal biological function without evidence of damage to surrounding genetic sequences.[3] In fact, there are several oligonucleotide "gene repair" strategies in preclinical development that have achieved a comparable result. These technologies presumably will not have the risks associated with gene transfer primarily because no gene transfer is involved. Therefore, substantial progress is being made toward answering the first major question, "Would the gene transfer methods mutate or perturb the genome, resulting in undesired inheritable consequences?" This progress is occurring due to a shift in focus from gene transfer to the development of new technologies for mutation repair.

TFBOs are oligonucleotides (short strands of DNA chemical bases) comprised of two functional components. One of these components is called a duplex-binding domain (DBD) because it is designed to bind to the normal double-stranded structure of DNA (duplex DNA), forming a three-stranded structure (triplex). The DBD is known to bind duplex DNA in a sequence-specific manner, thereby allowing precise targeting of the oligonucleotide to a known mutation. The DBD component functions essentially as a nonviral delivery system that targets the DNA strand to a specific DNA sequence in the genome. The second component, the portion attached to the DBD, is termed the repair domain (RD). The RD is constructed to contain the correct DNA sequence to "repair" the mutation. The sequence of the RD differs from the mutant DNA sequence only at the mutant base and functions as the template for correction of the mutation.

The oligonucleotides can be transferred (transfected) into cells using a variety of nonviral methods. Once inside the cell, they are transported to the nucleus. When the DBD binds to its target DNA sequence, it positions the RD adjacent to the mutant sequence. It is thought that the RD invades the duplex DNA, inducing naturally present DNA repair enzymes to restore the area's normal duplex structure. In a proportion of cells, the mutant base is replaced with the desired new base encoded by the RD. The "repair" of mutations with TFBOs in human primary lymphocytes has achieved an efficiency of 1 to 2 percent.

Data on two other gene repair technologies in human cells have been published. Small fragment homologous replacement (SFHR) is based on the use of short, single-stranded DNA molecules (300 to 500 chemical bases in length)

that are designed to bind to a specific DNA sequence that overlaps the mutation. This is essentially the RD portion of the TFBO, only with ten to twenty times more chemical bases. Following transfection of these short DNA fragments into cells, the fragments move to the nucleus, where they bind to a specific DNA sequence overlying the mutation. The binding of the SFHR to the target DNA sequence produces an irregularity in the duplex DNA structure around the mutation. Presumably, this binding event induces the innate DNA repair system to correct the DNA structure. Preclinical investigations have shown an efficiency of mutation correction of 1 to 10 percent in transformed and primary human respiratory epithelial cells.[4]

Third, RNA-DNA oligonucleotides are circular structures that contain both DNA and RNA unlike the TFBO and SFHR oligonucleotides. The short stretch of RNA bases in the midst of DNA is designed to bind directly to the mutation. It is both the sequence of the RNA bases and the sequence of DNA bases in the oligonucleotide that facilitate binding to a specific DNA sequence, overlapping the mutation. Following transfection, the RNA-DNA oligonucleotides travel to the nucleus, where they are thought to invade the double helix structure, binding to the target DNA sequence. It is hypothesized that this binding induces the innate DNA repair system to correct the DNA structure as suggested for the TFBO system. Estimated efficiencies have exceeded 10 percent in EBV-transformed human B-cells and in human hepatoma cells.[5] Efficiencies in primary human cell lines have not been published.

Importantly, none of these three gene repair approaches have reported adverse molecular consequences from the oligonucleotide transfections. This is not surprising since these are transient systems that serve to induce endogenous DNA repair enzymes to correct the mutation. Rather than inserting permanent viral vectors in the cell, the oligonucleotides are degraded within hours. Therefore, the utility for the clinical application of these gene repair technologies is limited primarily by the efficiency of the mutation correction event. Continued research should improve the efficiency, safety, and understanding of how to manipulate the DNA repair system to correct the targeted mutation preferentially.

The risk of aberrant, permanent genetic changes using oligonucleotide gene repair strategies is believed to be small for reasons discussed below. While the risk may not be zero, it is certainly less than the risk accompanying the use of integrating viral vectors for at least two reasons. First, the oligonucleotides are degraded within hours. As a result, treated cells would contain little or no ad-

ditional DNA at the time of reinfusion into the patient (ex vivo application). For in vivo application, the half-life will be limited to hours as well. Since the oligonucleotides are not expected to induce a neutralizing immune reaction, they can probably be administered repeatedly in vivo to boost efficiency. Second, the degree of sequence specificity for a given location in the genome is related to the number of nucleotides in the oligonucleotide. Longer oligonucleotides (more than twenty bases) are expected to have only one homologous sequence in the cell. Each of these oligonucleotide gene repair strategies is designed to be longer than twenty bases, the RNA-DNA oligonucleotides are usually at least twenty-five to forty bases in length, the TFBO oligonucleotides are commonly forty to ninety bases in length, and the SFHR fragments run around 300 to 500 bases in length. Since only a few mismatches between the oligonucleotide and the duplex DNA will destabilize binding, the risk of altering nonhomologous sequences would be extremely low with oligonucleotides of this length.

The relative risks of nonspecific sequence alteration could be ascertained in model organisms through the manipulation of embryonic stem (ES) cells (cells derived from embryos that can be grown in culture, genetically manipulated, and then reimplanted into animals to form new embryos) or embryos themselves. These methods would be very sensitive and useful for preclinical testing since it is not possible to survey the entire genome of the treated cell to look for extraneous point mutation changes. The treatment of ES cells would assess all of the genes required for complete development of a functioning organism. Mutations occurring in genes that alter the phenotype of the organism would be easily identified. Areas of the genome that are similar in sequence could be sequenced in the progeny for added confidence. Complementary experiments in human stem cells could also be performed to establish the safety of the gene repair system. The effects of the transfection reagents would be simultaneously tested in these systems. Study of human embryos would be limited to confirmation of the safety parameters established in animal models and human stem cells. Repeated human embryo research would not be needed for each new genetic disease since the only difference would be the length and sequence of the same four bases in the oligonucleotides.

The basic information needed to apply these unique oligonucleotide technologies is knowledge of the wild-type human genomic DNA sequence and the mutation that is to be corrected. Based on this sequence information, the oligonucleotides are designed and delivered to cells. Since the gene is to be re-

stored to a normal sequence, it is not necessary to know all of the factors that regulate gene expression as with gene transfer. Correction of the mutation in the existing gene restores cellular regulation without the need to transfer regulatory genes. In addition, these gene repair technologies allow the repair of mutations in regulatory genes that would be very difficult to correct by gene transfer, providing a significant advantage over traditional gene transfer.

The actual efficiency of gene repair required for clinical usefulness depends on the disorder. For instance, correction of a few percent of spermatogonia cells (cells that produce sperm) in an infertile man with azoospermia (absence of motile sperm) could result in a sufficient number of viable sperm for successful in vitro fertilization. Since no viral vectors are required, the treated cell is expected to be genetically identical to a normal cell after having changed a single chemical base to restore proper gene function. Sperm and spermatogonia cells collected from the treated man could be analyzed to determine if there is any evidence of deleterious effects induced by the treatment with oligonucleotides before fertilization. Since the mutation in this case precludes fertility, no human preclinical embryo experiments are possible. Further design improvements in the oligonucleotide structure (e.g., chemical modifications that increase the strength of binding), improved transfection methods, and full characterization of the treated cells may demonstrate that oligonucleotide gene repair strategies have the same or better risk profile compared to those of IVONT and SCNT.

However, even the exchange of one chemical base for another to correct a DNA mutation may have unappreciated risks for germ-line application. For instance, the transfer of genetic material (e.g., oligonucleotides) at a meaningful efficiency requires a carrier (transfection agent) and perhaps millions of DNA or DNA/RNA molecules to be transferred into the cell nucleus. The consequences of these procedures, both transient and permanent, have not been fully investigated. However, it has been observed that the treatment of cells with transfection agents used to carry antisense oligonucleotides, for instance, results in the induction of the production of nonspecific RNA molecules within minutes.[6] Therefore, it is difficult to predict how long it will take to develop safe and effective gene repair systems for human use.

## Using New Preclinical Studies/Safety Assessments

Before moving forward with germ-line intervention in humans, highly sensitive techniques for monitoring the effects of each reagent are needed to de-

termine which technologies are safe enough for IGM. We, the scientific community, have tended to oversimplify the biological effects of apparently innocuous, transient manipulations like transfection reagents because we can measure only a limited number of parameters in tissue culture cells. New, highly sensitive tools for measuring RNA changes in nearly all human genes are now available. A technology has emerged that utilizes microarrays (silica or glass wafers or chips with copies of gene fragments attached) that allow for the quantitation of RNA molecules from known genes. These microarrays can be used to assess cellular alterations in gene function instead of relying heavily on morphological and enzymatic measures. For instance, an RNA microarray containing thousands of genes has been recently used to identify differentially expressed genes (those genes where expression is elevated or decreased relative to each other) in multiple cancers. The results permitted a clear distinction of clinically significant subtypes of cancer not previously obtainable using traditional pathological methods for analysis.[7] As the development of protein microarrays mature, protein alternations may also be used to assess the effects of gene repair in cells.

The second major question, "Could scientists know enough about the functions of genes prior to initiating IGM to be certain that successful correction of the gene would not have associated deleterious genetic effects?" is being addressed by new information and technologies resulting from the Human Genome Project. Data are being gathered and shared through a variety of global genomic efforts, providing an unparalleled opportunity for understanding the genetic basis of disease. In addition, new technologies are growing out of this information, such as RNA microarrays and proteomics technologies, which provide an ability to discern subtle biological changes within cells that could not be discerned before. Without possessing this new genetic/genomic/proteomic information and associated tools, fully educated decisions about the potential consequences of germ-line manipulation are compromised.

It is expected that the treatment of cells with "transient" transfection systems containing oligonucleotides for gene repair will also rapidly induce changes in RNA expression. While RNA expression itself may last only minutes to hours, the proteins induced by RNA can last for days to weeks. While these changes are transient, the proteins induced by the reagents can have long-term consequences in the short life of an embryo, for instance. Herein lies a crucial issue regarding the treatment of spermatogonia compared to embryos. Once

the mutation correction has been effected in spermatogonia, studies to confirm the efficiency and safety of gene repair can be undertaken without a pressing need to move quickly. This procedure is similar to that of many approved somatic cell gene transfer experiments that use ex vivo gene transfer. Nonetheless, care must be taken to ensure that the potential deleterious effects of each component are thoroughly studied with methods sensitive enough to provide confidence in our understanding of the biological effects of the reagents.

RNA microarrays are manufactured using computer chip manufacturing technologies like modified photolithographic techniques to attach millions of copies of single-stranded DNA molecules on glass or silica wafers (chips). Using these techniques and knowledge of the human genome, all known expressed gene sequences can theoretically be represented on the chips.[8] The RNA from patients is labeled with a fluorescent tag and applied to the chip. A laser and a computer are able to read the relative amount of fluorescence coming from each gene on the chip, allowing for precise and sensitive measurements. Until this technology was developed, only a few expressed gene sequences could be studied at any one point in time. The ability to look quantitatively at alterations in gene expression for thousands of genes concurrently provides an opportunity to assess the effects of reagents on cells with a sensitivity and specificity far beyond current technologies. Importantly, the research does not need to speculate as to which genes should be treated ahead of time. Using microarrays, one can assess all of them simultaneously.

This new RNA microarray chip technology will soon be complemented by the development of "protein chips" that will allow the screening of changes in protein expression in cells and body fluids. A number of techniques are being investigated for the detection of proteins, including 2-D gel electrophoresis, mass spectrometry, and more recently the manufacture of protein chips for use in a manner similar to that of RNA chips.[9] Since antibodies can be produced with very high specificity and attached to "chips," the screening of all known proteins within cells is within the realm of possibility.

Together, these technologies allow rapid screening of human tissues treated with various DNA-targeted reagents to understand the subtle changes that are not attainable with current techniques. To achieve these goals, completion of the mapping of the human genome and proteome, within understanding of the function of each of the genes and proteins, is required. As the pace of genomic discovery and invention continues in the Human Genome Project, we can expect these technologies and as yet unpublished technologies to permit

even more precise analysis of the subtle effects of the genetic manipulation of cells. This capability should enable the development of safe technologies for intentional human IGM.

RNA microarray chips are also available for rats and mice. This availability will allow for a direct correlation of gene expression alterations between animal and human tissues. With these new sensitive techniques, we will move much closer to understanding the variety of potential consequences, positive and negative, associated with any gene therapy/gene repair technology for IGM. The question is no longer, can we find a disease in which we can justify attempting germ-line gene therapy using current techniques, but rather, can we use the new genetics/genomics tools to identify a safe basis from which to proceed?

To be successful in applying IGM to humans from the outset, the long- and short-term effects of the mutation correction technology will need to be correlated with proper animal and human cell model systems (i.e., cell lines, stem cells, primary tissues). Animals with genetic mutation(s) comparable to those of humans need to be produced. Gene knockout models fail to provide sufficient representations of human disorders, clearly exemplified in the creation of transgenic mice with mutations in the cystic fibrosis transductance regulator (CFTR) gene as models of cystic fibrosis. The studies have shown marked differences and similarities between the various knockouts.[10] Subtle changes in the DNA sequence can lead to altered proteins that may have new functions, unlike the gene knockouts commonly made in mice that eliminate the new protein function. Since animal models may still not mimic the human disorder, even with the proper point mutation, correlative studies in human stem cells are indicated.

The production and study of these animals will serve a dual purpose. First, the gene repair technologies under development for IGM can be used to make the point mutation animal models. In making the point mutation animal models, scientists will be studying the safety features of these technologies in the mammalian germ line. Second, gene repair technologies can be used to restore proper germ-line genetic function in order to observe the progeny of these animals for adverse consequences. Efficient, safe correction of the mutation in these models will complete a critical step toward human IGM application.

In addition to the production of transgenic mice, germ-line studies in animals have already confirmed the successful transplantation of spermatogonia, creating transgenic offspring.[11] Gene transfer experiments involving the tran-

sient transfection of marker genes into the spermatogonia of mice have confirmed expression of the transferred gene in vivo.[12] At a minimum, these examples in animal model systems represent a conceptual basis for IGM as a treatment for infertility. However, before human application, animals need to be produced that have the specific abnormalities intended for human therapy and the safety of the procedure needs to be carefully studied with the newer gene repair techniques.

Obviously, human stem cell experimentation would supplement the findings of animal experiments as well as confirm the safety and efficiency of mutation correction in human tissues. These experiments would also be integrated into the RNA microarray experiments, evaluating gene expression alterations for transient gene expression as well as gene expression alterations throughout differentiation of stem cells. The ability to assess these changes in human stem cells would substantially replace one of the important functions previously thought to be exclusively associated with human embryo research.

The ability to look at the subtle effects of oligonucleotide mutation correction technologies on cellular differentiation in stem cells should limit the need for human embryonic tissue research. Until such time as the safety parameters have been determined with the new genetic/genomic/proteomic techniques in animal and human stem cells, there will be limited need for human embryo research. Therefore, human embryo experimentation may be delayed a number of years and would then be used only to confirm data in human cell lines and animal models, but not serve as the primary research process for understanding the effects of oligonucleotide-mediated gene repair on multilineage differentiation.

## Selection of Disorders for Initial Clinical Application

Continued technological advancements will further improve the possibilities for safe and effective correction of disease-causing DNA mutations, allowing for the elimination of disease manifestations. By proceeding with caution and emphasizing the need to leave the cell genetically "normal," rather than adding genetic material, germ-line manipulation begins to look more like a potential therapy.

As technological advances continue, disorders in the human germ line must be reconsidered as candidates for clinical application. It would be wise to begin with what may be the most morally acceptable first experiment, the selec-

tion of a mutation that is the basis for infertility. A specific mutation has been identified in several men that leads to azoospermia and infertility. The gene is called ubiquitin-specific protease 9 (USP9Y).[13] One specific mutation in USP9Y that causes the lack of motile sperm is a deletion of four chemical bases. This deletion leads to a shortened, nonfunctional protein. Correction of the mutation in testicular spermatogonia cells presumably will lead to motile sperm that could be used for in vitro fertilization. The USP9Y gene is just one example. It is expected that many more mutations leading to infertility will be identified in men and women over the next few years.

Advantages of targeting infertility in males are as follows:[14]

1. Correction of the defect requires only the repair of the spermatogonia cells. Systemic application would not be needed. Theoretically, both in vivo and ex vivo applications of gene repair technologies could be used if the spermatogonia can be grown in the laboratory.
2. Successful correction of the mutation in the spermatogonia would result in motile sperm that could be analyzed at the molecular level before fertilization is attempted.
3. Conducting this work as part of an approved in vitro fertilization (IVF) program may provide additional confidence in the safety of the procedure due to the use of established and validated techniques.
4. A high efficiency of mutation correction would not be absolutely required since a limited number of sperm could be used for in vitro fertilization, and no human embryos with the mutation are available.
5. One could genetically analyze the embryo during the in vitro fertilization process if indicated.

The actual clinical procedure will likely vary somewhat by the time the experiment would be approved due to new information obtained in the interim. However, the clinical process might occur in the following manner.

A man with infertility due to a specific mutation such as a deletion of four chemical bases in the USP9Y gene would be identified. After signing an informed consent document, he would receive an intravenous infusion of oligonucleotides that had been used successfully to correct the mutation both in mice and in his cells in the laboratory. The intravenous infusion may be systemic or be selectively delivered into the regional blood vessels of the testicles. A testicular biopsy and sperm would be collected and studied for evidence of mutation correction, sperm motility, and any evidence of abnormality as a con-

sequence of the procedure. If all of the studies were without problem, an in vitro fertilization step could then be undertaken with his new motile sperm. For added confidence, the embryo could also be molecularly evaluated before implantation. Since this procedure does not require the correction of a disease genotype, there would be no particular monitoring other than to note the correction of the mutation in the somatic cells and germ-line cells of the child.

Since the goal of this hypothetical paradigm has been to obtain a level of safety for IGM that matches or exceeds the risk/benefit ratio associated with IVONT or SCNT, why not transfer nuclei instead of implementing the gene repair procedure outlined above? While the transfer of a "nonmutant nucleus" from one cell into one containing the mutation may eliminate the mutation, the process is discarding the hereditary material of the recipient. Few people are going to favor this option, since they want their child to be "their" child. While there will be circumstances where IVONT and SCNT will be chosen, these techniques will not be applicable to all situations.

Prospects for application beyond infertility will benefit tremendously by a successful beginning for a disorder such as azoospermia caused by a mutation in USP9Y. Classical thinking suggests that genetic disorders that have the onset of a severe, irreversible phenotype in utero would be the logical choice for early experimentation. While the most severe phenotypes, not treatable by the standard treatments of the day, should be the first disorders targeted for treatment, a second consideration, the different technological obstacles between loss of function and gain of function disorders, must be considered. If the disorders are due to an overexpression of a mutant gene, then very high levels of gene correction will likely be needed. With lower efficiencies of mutation correction, some mutant cells will remain and may cause disease, depending on the biological processes involved. In the case of loss of function, much less than 100 percent correction will likely have significant clinical benefit.

A third issue in moving beyond the infertility genes in spermatogonia is to identify those tissues and disorders that have technological issues similar to those involved in the initial applications in spermatogonia (e.g., type of mutation). If oligonucleotide gene repair technologies are used initially, there will probably be little difference in the oligonucleotide design between disorders. However, specific tissue effects may be very different between tissues and another set of safety studies would be indicated (for example, if targeting the female ovum instead of the spermatogonia).

In summary, the technological foundation for progressing in a logical, care-

ful, and safe manner toward the initiation of germ-line genetic manipulation is present. A logical starting point, male infertility, has been identified based on our current understanding of the human genome. Considering the new technologies available and rapid pace of advancement, one can envision holding germ-line manipulation to a higher standard, one that should be at least as safe as IVONT without encountering enormous delays. While we may feel a need to rush in developing therapies for those who currently suffer without satisfactory treatments, IGM, unlike somatic gene cell therapy, has consequences far beyond the treated individual. Patience and thoroughness in fully developing these new technologies is indicated. The time course of the first clinical trial is dependent on further technological development, improved gene repair efficiency, assessment of subtle reagent effects, and reaching an understanding that a specific clinical disorder is a reasonable place to begin from ethical, scientific, and social perspectives.

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CHAPTER SEVEN

# Germ-Line Gene Therapy

## Can We Do It, Do We Need It, Where Do We Start, and Where Might It Lead?

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Despite several setbacks, somatic cell gene therapy is finally beginning to record some solid clinical successes.[1] There is growing optimism that such an approach to the treatment of disease will indeed prove fruitful, and somatic gene therapies for a variety of disorders, both genetic and nongenetic, lethal and nonlethal, are at advanced stages of development. As this former frontier of genetic medicine becomes increasingly commonplace, the leading edge of novel therapeutic intent will continue to expand and challenge new boundaries. One of these, germ-line gene therapy, is already beginning to evolve, in certain quarters, from the realm of the undoable and unthinkable, to that of the possible and desirable. Indeed, it is increasingly suffused by an air of inevitability. This chapter, written during the early stages of this transition, examines whether intentional human inheritable genetic modification (IGM) is indeed scientifically possible and medically necessary, and attempts to identify clinical settings where it might be applied, both initially and ultimately. No attempt is made to address societal, moral, religious, or other nonscientific elements of IGM, which are dealt with elsewhere in this volume.

## Can We Do It?

IGM is clearly possible—scientists have been doing it in mice for more than twenty years.[2] The real question is whether it can be achieved in a manner that may be responsibly applied to people for noble purposes. Germ-line gene therapy places severe constraints on the technologies that should be used to achieve the required germ-line modifications. Existing approaches to gene transfer and gene modification have been reviewed in Chapters 3 and 4 in this volume.

Somatic cell gene therapy traditionally involves gene supplementation rather than gene replacement or repair. In gene supplementation the offending mutations are not eliminated, but instead their effects are masked. This approach is workable for most recessive loss-of-function disorders. It could also be useful in dominant gain-of-function disorders if reliable methods could be developed to silence mutant alleles. However, there are two good reasons why gene supplementation approaches are not appropriate for germ-line applications. One is the persistence of the mutant allele, which could segregate from the transferred therapeutic gene in subsequent generations so that the disorder would reappear. The other reflects the probability that the foreign genetic material introduced into the modified genome will prove harmful. This is a particular concern when using vectors, such as retroviruses, which integrate into the genome at random locations. The nature and incidence of the abnormalities that may result from such events is hard to predict, but large percentages of transgenic mice have mutations and associated problems. More precise data may be forthcoming with the increasing use and scrutiny of genetically modified crops and farm animals[3] because, unlike mice, we eat them or their products. Even when the additional genetic information is introduced as an episome or artificial chromosome, there are concerns about long-term, transgenerational safety. Given such uncertainties, it would seem prudent to restrict IGM, if indeed it is to go forward, initially to gene replacement or correction. Strategies for achieving this include homologous recombination and gene repair.[4]

Kenneth Culver, in Chapter 6 in this volume, reaches a similar conclusion and reviews the present state of the art regarding gene correction technology. This remains at an early stage of development, but there is the probability that efficient methods will emerge. Once they have done so, and been shown to work safely in human somatic cell gene therapy, there will be pressure to use them for intentional IGM.

If IGM were to be used in humans, it is possible that genes would initially be modified in zygotes by ex vivo strategies coupled with in vitro fertilization (IVF) procedures. In this case, techniques for achieving efficient gene correction or replacement will need to be adapted from their present development in somatic cells to the rather different circumstances of the fertilized egg. Germinal stem cells[5] provide an alternative and possibly simpler target of use when the father's genome carries the targeted mutation. Because these cells can be grown in tissue culture and divide indefinitely, cells containing the appropriate genetic modification might be readily selected. Furthermore, the production of the appropriately modified sperm can be confirmed prior to conception after the corrected stem cells have been returned to the donor or a laboratory animal. The genetic modification of oocytes has been less investigated, although the direct microinjection of DNA into eggs has been a common experimental technique for some time.[6] It is complicated by the limited numbers of oocytes that a woman can provide, even when superovulated. Spermatozoa, in contrast, are abundantly available but there is little literature to suggest how they may be genetically modified in a safe and reproducible manner.

Instead of genetically modifying the germ-line cells themselves, it may prove possible to make use of embryonic stem cells or even somatic cells from one parent. Fertilized eggs would be allowed to develop in vitro to the blastocyst stage and used as a source of embryonic stem cells.[7] Because these cells divide indefinitely and can be expanded in tissue culture, selective expansion of appropriately modified cells is possible. Efficient methods will need to be developed for the implantation of the modified cells in such a way as to develop an embryo in which all cells carry the corrected gene, rather than a mosaic, as is the case with mice. Ethical concerns surrounding the growth and discarding of a blastocyst as a source of embryonic stem cells might be obviated by use of a parent's somatic cell—but the cloning that would be involved generates more moral problems than it solves. Nevertheless, it looks increasingly likely that embryonic stem cells derived from such cloning procedures will provide the starting point for intentional human IGM. The techniques for generating embryonic cells in this way are becoming increasingly refined, and the cells are readily amenable to genetic modification.

Thus, returning to the original question, IGM is clearly possible but the technologies that would permit its responsible human application remain inadequate. There is, however, every possibility that the necessary techniques will become available within the next five to ten years. It is likely that they would first be used to correct genes in embryonic stem cells.

## Do We Need It?

Although the eradication of harmful genes from the germ line may be a good thing, IGM is not the only way to achieve this. A particularly successful, inexpensive, and low-technology example is provided by the eradication of thalassemia from Cyprus.[8] Couples were screened for the presence of mutations in their globin genes, and those at risk of producing affected offspring received counseling. Similar tactics were successful in reducing the incidence of Tay-Sachs disease among the Jewish population in New York.[9] This is not to suggest that all genetic diseases can be approached successfully in this way, but it does illustrate the effectiveness of one low-technology, relatively simple modality.

An alternative strategy, which does not involve IGM, combines in vitro fertilization (IVF) with the preimplantation selection of zygotes.[10] In this procedure, eggs are removed and fertilized in vitro. Individual cells are removed from the resulting zygotes at the eight-cell stage and tested for the presence of the mutation in question. Zygotes lacking the mutation are then implanted into the mother, secure in the knowledge that the resulting child will not have inherited the condition. In theory, this strategy will work under all circumstances except those where both parents are homozygous for a recessive trait or where at least one parent is homozygous for a dominant trait. In practice, it will also not help those with moral objections to certain elements of the IVF and selection process, such as the discarding of unused zygotes.

Instead of selection after fertilization, it may prove possible to select eggs and sperm before conception. Although this is not yet possible, progress is being made. With oocytes, for example, it is possible to conduct polymerase chain reaction (PCR) analysis on the first polar body released after the first meiotic division.[11] Although this does not provide a definitive answer, it could be used in conjunction with other types of assay for greater precision. It may be possible to separate sperm carrying the X chromosome from those carrying the Y chromosome,[12] but beyond that the selection of sperm on the basis of genotype is not presently an option.

Finally, it needs to be appreciated that advances in conventional therapies continue to occur at a rapid rate and may reduce the burden of certain genetic diseases to such a level as to compete with eventual germ-line gene therapies. Ironically, somatic cell gene therapy may be one such competing therapy. Indeed, the very technological advances that would facilitate the development of

IGM could well be those that would make somatic cell gene therapy so safe, efficient, and inexpensive as to obviate the need for germ-line manipulations in many instances.

## Where Could We Start?

Because IGM raises such emotive and complex issues, discussed elsewhere in this volume, the selection of the first disease target is critical. It should be selected from among the group of monogenic disorders that are well understood genetically, biochemically, and clinically and possess a well-established mode of inheritance. Ideally, it should be a disease that is only treatable by germ-line gene therapy. It would be:

1. poorly responsive to existing treatments
2. serious enough to merit experimental procedures
3. carried or present in prospective parents for whom alternative options, such as preimplantation zygote selection, would be ineffective

Few candidates meet such demanding criteria. One obvious circumstance satisfying these three conditions occurs when both parents are homozygous for a genetic condition. However, the disease would now need to be sufficiently mild or treatable to permit survival to the age of sexual maturity. Certain patients with Gaucher disease, sickle cell anemia, or even cystic fibrosis might provide eligible candidates, given the continued improvement in conventional therapy. Nevertheless, the number of such cases would be vanishingly small. If such couples could be found, a successful germ-line therapy would provide proof of principle and certainly add to the quality of family life for the couple in question, but would not meet a major unfulfilled medical need.

An alternative possibility is presented by couples where the prospective father is a carrier of an autosomal recessive disorder and the mother heterozygous or homozygous for the disorder. This couple may wish to eliminate the possibility of having an affected child without using IVF and preimplantation zygote selection. Such couples may, for instance, have moral objections to the process. However, they may not object to genetic modification of the male germinal cells, as no embryos are created or discarded. Germinal stem cells could be removed from the father, genetically corrected in vitro, selected, tested, and expanded in culture. Ideally, the corrected germinal stem cells would be returned to the father under conditions where those germinal stem cells that were

not removed at the beginning of the procedure do not contribute to sperm formation before fertilization. Until this is possible, the corrected germinal stem cells might be implanted in a suitable laboratory animal that would now produce the genetically corrected sperm of the father. Under these circumstances, the sperm would be harvested and tested, and conception achieved by artificial insemination. With the mutant gene eliminated from the father's sperm, no affected child can result and the worst outcome would be a child who is a carrier of the mutation.

Certain male infertility disorders have been suggested as possible initial candidate diseases by Culver (see Chapter 6 in this volume). Approaches to the gene therapy of these conditions also involves correction of the male germinal cells. In the example provided by Culver, a mutation in a gene on the Y chromosome encoding ubiquitin-specific protease 9 renders the patient infertile. Using existing technologies, sperm could be withdrawn from such individuals for IVF, assuming that the lack of motility is not a barrier to fertilization by intracytoplasmic sperm injection, and female zygotes selected for reimplantation. Alternatively, it may prove possible to select sperm carrying the X chromosome with which to fertilize the egg. However, if the father wished to conceive a normal son, this procedure would not help although it is important to note that any male offspring would, like the father, be otherwise healthy and able to reproduce via IVF. Nevertheless, for the reasons discussed in Chapter 6, diseases of this type hold several advantages in seeking candidates for the first application of intentional IGM in humans.

Although IGM may prove successful in helping individuals of the types described above, such cases are rare. Under present circumstances it is unclear whether it would find wide applicability in the eradication of monogenic diseases, a conclusion that raises further issues of cost-effectiveness. Nevertheless, there are certain possible future scenarios where IGM could have a huge impact on human health.

## Where Might It Lead?

Classical single-gene defect diseases are uncommon. Western societies are most afflicted by complex, polygenic disorders with important environmental and stochastic components including cancers, cardiovascular diseases, neurodegenerative diseases, infections, and a variety of disorders of the muscu-

loskeletal system. Despite the best efforts of the medical research community, many of these diseases remain resistant to effective treatment. They might eventually turn out to be the best targets for germ-line gene therapy. Two approaches can be envisaged. One of these targets disease susceptibility genes. The other attempts to provide individuals with extra copies of inducible genes encoding therapeutic products.

We are witnessing an explosion in the identification of genes that predispose individuals to particular diseases. Examples include mutations in the breast cancer (BRCA)-1 and -2 susceptibility genes for breast cancer, the retinoblastoma gene, APC for familial adenomatous polyposis, the angiotensinogen (AGT) gene for cardiovascular disease, and the ApoE gene for Alzheimer disease. As the human genome project nears completion and efforts to detect and understand single nucleotide polymorphisms accelerate, the number of genes and gene polymorphisms that are known to influence our susceptibility to various diseases will become very large. Under these conditions, germ-line gene therapy, using techniques perfected and validated in the manner discussed in earlier sections of this chapter, could be used to reduce the risk of the recipients developing the diseases in question. Because of the large numbers of people that could potentially benefit from such interventions, the laborious, expensive, ex vivo procedures outlined in the previous section are impractical. Altering susceptibility genes needs to be approached carefully, because the genetic background of the patient may influence the outcome in important ways, and some polymorphisms that protect against one disease may increase susceptibility to another. An example is provided by polymorphisms that alter the expression of IL-10 and TNF. Patients with a "high IL-10, low TNF" profile tend to be protected from rheumatoid arthritis, but to be more vulnerable to infectious diseases and vice versa. Nevertheless, there are several examples, such as the BRCA gene mutations mentioned above, where reversal to wild-type would be expected to provide a clear benefit.

The second approach draws from the identification of genes whose products provide protection from disease. Examples include tumor suppressor genes in cancer, IL-1Ra for rheumatoid arthritis, and γ-IFN for infections. Although the genomes of all individuals already contain these genes, the diseases they combat nevertheless occur frequently, and there is evidence that administration of the gene product is therapeutic. However, traditional methods of protein delivery are inefficient, expensive, invasive, and cumbersome. Equip-

ping us all with extra copies of these genes, whose expression could be easily and independently regulated, would provide a very effective, novel therapeutic strategy. This involves introducing additional genetic elements into the genome, an approach that was not encouraged in the earlier section discussing how IGM might move forward in its initial stages. However, it is expected that by the time the field has progressed to the point of entertaining the present suggestions, methods for the safe insertion of additional genetic material will have been developed. Such methods might include the use of artificial chromosomes or self-replicating episomes, or rely on the identification or engineering of safe docking sites in the existing genome.

Because of the high cost to society of the diseases that might be eradicated by these types of IGM approaches, the cost-benefit argument lies in their favor, so long as competing therapies do not intervene to alter the equation. Both of these future possible uses of IGM can be construed as examples of genetic enhancement, as opposed to therapy, and will provoke vigorous debate. Those issues are discussed elsewhere in this volume.

## Conclusions

Strange as it may seem, germ-line gene therapy may have little impact on the treatment of classical monogenic, Mendelian disorders. However, the few cases that are handled in this manner will be important, because they will allow rigorous proof of principle to be established in terms of efficacy and safety, as well as increase the comfort level among the biomedical community, and society at large, in performing IGM in humans. This could serve as a prelude to its much wider application in improving our ability to prevent and treat large numbers of very common diseases. Clinical trials to assess the efficacy of IGM in these diseases will be complicated, because many of them do not occur with high frequency until middle age and there is a stochastic element to their occurrence. Thus, large numbers of individuals might have to be followed for such long periods of time that the originating investigators may no longer be alive. Considerable technical limitations need to be resolved before any of this can take place, but the rapid and increasing rate of progress in genetic technology during the past decade suggests that this will happen sooner than many of us expect. Whether these technologies should be permitted in humans is a separate question, which cannot be answered by science alone.

NOTES

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CHAPTER EIGHT

# The Moral Impasse in Human Embryo Research

## Bypasses in the Making?

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In some cases, new technology creates a bypass around a seemingly intractable moral impasse. For example, before it was possible to diagnose death by neurological criteria, justifiable caution blocked the way to saving lives by transplanting organs from brain-injured patients presumed to be dead. This caution was due to uncertainty about whether patients on ventilators whose hearts were still beating were truly dead.[1] Diagnosis of death by neurological criteria (clinical signs assisted by encephalography) bypassed this obstacle and provided a technical solution to satisfy the rule that an organ donor must be certifiably dead before any procedures related to transplantation could begin. Furthermore, this advance optimized chances of success by reducing ischemic damage to the donor organ, which could be perfused right up to time of surgery.[2]

This chapter discusses the potential of two technology-assisted ways around the controversy over human embryo research (HER), which is a moral problem that divides our society and its politics. These bypasses *may* be in the making. Please note the emphasis on "may." The first could fail to prove itself and the second is very futuristic. These technologies could also evolve into other

possibilities. This chapter examines the following questions: How viable are hopes that there may be ways around HER? What morally defensible alternatives exist if these hopes do not materialize?

## Two Bypasses in the Making?

Stem cells are unique inasmuch as they renew themselves and give rise to specialized types of cells in the human body (e.g., blood, bone, muscle, neural, etc.). Stem cells found in the human embryo are pluripotent (i.e., infinitely renewable and the progenitors of most of the cells functioning in the human body). These characteristics make scientists and patients hope that cell lines grown from embryonic stem cells will be an ideal source of therapy for diseases caused by cell wasting or cell death. Human embryonic stem cells (ESCs) in current research[3] are almost universally derived from clinically unused embryos donated by couples in infertility treatment. The act of deriving ESCs for research destroys the embryo. Communities or persons holding that embryos have the same right not to be killed accorded to a living fetus or individual obviously regard such an act as morally wrong. Without belaboring all sides of the moral debate about HER, if there were a way to avoid the use of ESCs for research and treatment, it would greatly reduce social conflict.

The first possibility for a bypass is using cell lines grown from adult stem cells (ASCs) or other less morally problematic alternatives, such as embryonic germ cells (EGCs) derived from fetal tissue after elective abortion. If these sources prove effective in therapy, then using ESCs may become unnecessary. Opponents of embryo research make this argument, and some argue that advances in ASC research have already rendered ESC research unnecessary.[4] On the other hand, the prevailing consensus in the scientific community is that this judgment is entirely premature and that the better course is to pursue parallel research with all three types of cells. As the most current and comprehensive scientific review of the entire field of human stem cell research concludes: "Predicting the future of stem cell applications is impossible, particularly given the very early stage of the science of stem cell biology. To date, it is impossible to predict which stem cells—those derived from the embryo, the fetus, or the adult—or which methods for manipulating the cells, will best meet the needs of basic research and clinical applications. The answers clearly lie in conducting more research."[5]

This judgment reflects no change in the prevailing view in the scientific community as reported by Vogel more than a year earlier: "most scientists caution that

research on both adult and embryonic stem cells is too premature to compare the potential of the two."[6] I will argue below that the only morally defensible way to create a bypass of HER in stem cell research is to proceed with parallel studies of cell lines grown from these three sources to determine their properties and their preclinical promise as cell replacement therapies. Several outcomes are possible: one source may be clearly superior in all cases; each source may be effective for specific diseases; or none will in the long run prove therapeutic.

An optimal moral choice would require the most scientifically rigorous answer to the question about the differences between these sources and their potential benefits to human beings, unless seeking the truth in this particular case would deeply violate values that make research in a democratic society ethically acceptable. The argument against HER is that such activities are irreducibly immoral based on an absolute moral duty not to destroy embryos, even frozen embryos that will be otherwise discarded, based on an exceptionless duty to respect and protect human life in all of its forms. However, this claim is overstated and is not a cornerstone of research ethics in this society. Furthermore, some conservatives support ESC research, despite violation of their principles. President Bush's policy allows some taxpayer-funded research on ESCs to proceed, especially involving clinically unused embryos donated by infertile couples who have consented to this possibility. To use a metaphor of travel, in the interim of discovery as science proceeds to explore possibilities of bypassing human embryos as sources of research and therapy, society is obligated to find a moral road that reduces to a minimum the degree of offense that any HER causes to its opponents. Additionally, since moral choices require reliable and truthful information, the science that ought to inform moral and public policy choices ought to be as complete as possible.

When I began writing this chapter in early 2001, I proposed a politically viable compromise to meet these tests, namely, to allow a trial period for National Institutes of Health (NIH) guidelines developed by the Clinton administration for funding ESC research. Essentially, NIH would be permitted only to do research "downstream" from the derivation of ESCs by industry-sponsored research, and no taxpayer funds would be used to destroy embryos. The NIH could, however, fund research on ESCs under strict standards showing proof that the sole permissible source was frozen embryos, scrupulous consent procedures for the parents, and statements from parents showing that they understood the purpose of ESC research. After his election, President Bush ordered the NIH to defer implementation of the guidelines pending a White

House review of the issues. After several months of internal struggle, the Bush administration outlined a policy on federal funding of ESC research that it estimates will not alienate the majority of its conservative constituency but still be responsive to the therapeutic promise of this research.[7]

On August 9, 2001, President Bush announced a very limited compromise allowing federal support for research only on *cell lines* grown from ESCs derived from frozen embryos by infertile parents who voluntarily donated them for research before August 9, 2001.[8] The Bush policy forbids any further federal funding of any future cell lines, and it draws a moral line between permitting knowledge to be gained from the "life and death" decisions over which his administration had no control and a moral position that society is obliged to protect embryos from harm or death in research activities, despite the promise of knowledge to be gained. The Bush position is one of moral compromise, since it acknowledges that the policy will seek benefits from embryo destruction and it breaks with a position so rigidly opposed to HER that it would forgo the opportunity to seek knowledge from even one embryo destroyed in research at any time.

In addition, Bush announced that a new President's Council on Bioethics would oversee ESC research. The council will be headed by Dr. Leon Kass, a conservative bioethicist. At this writing, the members have not yet been selected, nor has the body been chartered. This body will replace the National Bioethics Advisory Commission (NBAC), which was appointed in 1995 by President Clinton. The new council's concerns will not be restricted to ESC research but extend to a broader agenda related to the new biology and genetics. This process will require valuable time and delays in ESC research, a moral and political issue discussed below.

A survey conducted by the NIH's Office for Science Policy claims to have found sixty cell lines extant in laboratories in the United States and other nations that met Bush's criteria for procurement, which apparently will permit the use of fresh as well as frozen embryos donated by parents in a less complex informed consent process than the one required by the NIH guidelines.[9] Many scientists question this figure and have qualms about the quality and availability of these cell lines, especially those grown in non-U.S. laboratories. Because of difficulties in maintaining the viability of ESCs in mouse research, many federally funded scientists believe that this number will be too small to complete the research necessary to examine the properties of ESCs and compare their potency for therapeutic uses with other sources.[10] However, Dr. James Thompson, the first scientist to report the successful growth of cell lines from ESCs,

stated that he is satisfied with the president's policy and believes that sixty cell lines will be sufficient to allow "much to be done."[11] The administration's policy will be challenged in the Senate by Democrats and some moderate Republicans, but the political mood among senators who backed a stronger policy permitting the NIH to derive ESCs and grow cell lines from donated frozen embryos will probably be willing to "wait and see" what short-term scientific progress results from the administration's approach.[12] The strength of congressional opposition to the Bush proposal has yet to be measured.

The second possibility for a bypass of HER is distant but perhaps has a greater likelihood of success; that is, new genetic technologies may make it unnecessary to use affected human embryos for interventions in the human germ line to prevent inherited diseases. If such technology could correct harmful mutations in gametes or their precursors, there would be no need to do gene targeting to alter the DNA in the embryo's nucleus to create inheritable genetic modifications (IGM), except for genetic problems known to occur after fertilization, such as genetic imprinting. An American Association for the Advancement of Science (AAAS) report, cited below, recommends use of the term *inheritable genetic modification* rather than *germ-line gene therapy or engineering* because: (1) the public does not understand the term *germ line,* and (2) the term *therapy* is both inaccurate and misleading. There is no individual present to treat, and the term *therapy* is a misnomer. What research may deliver is *prevention* of genetic disease in the future individual and his or her descendants. "Therapy" also misleads because it leapfrogs all of the research and controversy required to bring about success, failure, or something in between. Gene targeting with embryos was recently discussed by Capecchi[13] and extensively by Resnik, Steinkraus, and Langer.[14] If IGM were proved to be safe and effective in gametes, most gene targeting in embryos could be unnecessary.

If realized and affordable, these two possibilities would create utopias for the sick and persons at higher risk to transmit genetic diseases. Cell-replacement therapy for diseases caused by cell injury or death would relieve immense suffering in the human population. IGM would prevent transmission of grievous burdens of heredity in families and in the larger population.

## Background of Topics

These two topics are obviously current. Two national bodies recently issued reports on the ethical issues of human stem cell research.[15] As a member of the

AAAS Germ Line Intervention Project working group's study of the scientific, ethical, and regulatory issues of IGM,[16] I was assigned to explore how the debates about HER and IGM intersected. At the outset of its deliberations on issues in human stem cell research, the NBAC invited a paper on the morality of deriving stem cells from each of four possible sources: embryonic germ cells derived from fetuses after abortion or ESCs derived from donated embryos, from embryos created for research, or from cloned embryos. NBAC sought guidance on how it should deliberate on the ethical issues, and also on whether NBAC should recommend that Congress amend its legal ban prohibiting federal support of HER to permit federal funds to be used for derivation of ESCs.

In the process of writing the NBAC paper,[17] my moral and political position on HER changed. This change altered my approach to the assignment for the AAAS IGM project. I became persuaded that HER should be used only as a *last resort* to learn whether cell lines derived from ESCs would be therapeutic in the context of diseases caused by cell injury or cell death. Previously, I had been a staunchly liberal advocate of HER and federal support for this activity. My views agreed with the report of the National Institutes of Health (NIH) Human Embryo Research Panel (HERP) in 1994, which strongly recommended federal support of HER.[18]

In a similar vein, I had long argued to keep a window of scientific freedom open for preclinical and animal research on IGM.[19] I assumed that embryos of parents at high genetic risk would be used in experiments with IGM aimed to correct harmful mutations. New genetic technologies may make these experiments unnecessary. The values at stake in these issues are respect for the intrinsic value of human life and fairness to those who might benefit from cell-replacement therapy and from prevention of hereditary diseases that IGM, if safe and effective, could bring. If we can achieve good therapeutic and preventive results and also minimize or prevent harm to human embryos, then why not pursue such a moral strategy?

## Lessons Learned in Defending Human Embryo Research Too Strongly

Readers of this volume need no lengthy review of the scientific or ethical aspects of human stem cell research. Hopes are high that this research will lead to cell-replacement therapies for a host of diseases caused by cell death or injury.[20] However, scientific and moral obstacles temper these hopes. The field is

still in an early scientific stage. Also, destroying embryos to derive stem cells is morally very controversial in the United States. Many people sincerely believe that embryos have the moral status of human beings and ought not to be destroyed, even to benefit those who would otherwise be disabled or die.[21] To show its displeasure with the HERP report, Congress in 1996 prohibited the use of federal funds for HER of any type.[22] Insofar as federal law is an important moral voice, one ought to interpret this ban to mean that destruction of embryos is a deep moral offense to many citizens represented by the majority in the House of Representatives in 1996 until the present.

How much weight and respect ought proponents of HER give to the opposing moral view? In the past, I gave very little weight or respect to such views. Unwilling to compromise my position, I simply argued that the status of embryos was "symbolic" in nature and that no harm could be done by research with a preimplantation embryo that would never be used for reproduction. Moreover, respect for embryonic life could only be shown in the restrictions and limits to be placed on HER. No scientist ought to enjoy absolute freedom to do anything with a preimplantation embryo, because of its human origins. But in my view, no intrinsic reason blocked valuable research that could not be done without HER. I gave the HERP report my strong support and criticized its opponents for setting the field back.[23]

The HERP report gave moral approval to research with two types of human embryos: (1) donated embryos remaining after infertility treatment for research, and (2) embryos created for research to answer important scientific questions that could not be otherwise explored. A colleague in pediatric oncology and I wrote a paper for the HERP arguing that HER was justified, among other reasons, to understand the causes of pediatric cancer.[24] For example, to explain the genetic action and pathophysiology of Beckwith-Weidemann syndrome[25] and retinoblastoma[26] would require study of affected embryos created for this purpose. Without such knowledge, we saw any attempt to prevent such cancers by IGM as a poorly informed "shot in the dark" that would violate the truth-seeking norm, among other norms and values, which guides the relation between science and this society. We anticipated that gametes from parents at risk to transmit such disorders would be needed to create embryos to study such questions. Although the panel's report did not endorse our examples, it cited our paper in the context of opposing any ban on fertilizing oocytes for research "of great scientific and therapeutic value and for which an adequate number of embryos is essential to assure validity."[27]

The panel's moral arguments and recommendations for federal support for HER met with strong opposition. Before the report was released, President Clinton rejected the possibility of federal support for creating embryos for research but accepted the recommendation to use "spare" embryos.[28] Congress followed by imposing a total ban on federal support for any forms of HER. Even those sympathetic to some forms of HER harshly criticized the panel's moral reasoning in the bioethics literature.[29] What lessons could be learned from this broad-based opposition? And what was the relevance of these lessons to NBAC's tasks?

The NBAC faced the same two ethical questions addressed by the HERP. Can it be ethically acceptable to destroy human embryos, even in a promising context, to study the properties and potential of ESCs for therapy? Is there a morally meaningful distinction for research ethics between using embryos donated by couples in infertility treatment and embryos created for research only?

The moral answer to the first query can only be a straightforward "yes" or "no." One either permits HER with embryos (with or without safeguards and oversight) or one opposes it. The sources of these answers are complex: (1) disparate moral views on the status of embryos, (2) differing interpretations of the extent of society's obligation to protect embryos and fetuses, (3) different worldviews that inspire moral ideas, and (4) different evaluations of the interests of parents in donating embryos for research. The important point is that there is no ground on which to compromise about the basic morality of HER. To a resolute conservative, it makes no difference whether the embryos are donated or created, for to permit any HER at all means sacrificing the lives of human beings in research. Liberals are the only ones who divide on the issue of the importance of the distinction between using excess embryos that would be discarded or embryos created only for research. In the liberal view, the only meaningful questions are how to restrict HER with safeguards to prevent abuses, or to fashion an oversight system.

However, as in the case of abortion, inability to compromise on basic morality does not mean that some compromises by moderate conservatives and liberals are not possible. Exceptions include abortion to save the mother's life, or abortion in the cases of pregnancies caused by rape or incest. In this vein, the NBAC's report[30] on ESC research builds on the work of Ronald Dworkin about abortion.[31] Dworkin showed that, despite their harsh rhetoric about basic morality, these compromises reveal that many conservatives are willing at times to put the interests of the living above the interests of the fetus. Following

Dworkin, NBAC argued that in the case of ESC research, many conservatives could be persuaded to make exceptions to their opposition to HER in the hope of saving lives and preventing disability. An example of moderate liberals compromising on a similar issue occurred with the passage of a stringent federal law on fetal research that rendered research with any degree of risk to the fetus virtually impossible.[32] Senator Albert Gore led the Democratic support for this bill.

Using the Dworkin argument, the NBAC opened the door to the possibility of compromise on federal funding for ESC research, but it did not walk through it. It failed to answer an objection that conservatives were certain to make to the use of the Dworkin argument. Namely, the benefits of saving lives and preventing suffering are very clear in the abortion exceptions, but ESC research is so young that one cannot predict with certainty that its benefits to persons will be comparable to those of abortion in exceptional cases. Also, since ASCs are already being used to treat some diseases, there are those who argue that ASCs have already bypassed the need for ESCs. Vogel reviewed the situation in ASC research and concluded that this view of ASCs was completely premature.[33]

Uncertainty about the future of ESC research and the potential for alternative sources are sufficient reasons to take a different road to the issue of federal funding than the one taken by NBAC or the Bush administration. In short, to reduce the degree of moral offense to conservatives done by HER and to liberals committed to an accelerated pace of discovery it is essential to gain more scientific understanding of ESCs and to ensure a timely process for NIH funding of preclinical work comparing the properties of ESCs, ASCs, and EGCs and their potential for treatment of human diseases. If preclinical work with ESCs proves the concept, then moral and political compromise would be possible between moderate conservatives open to an exception for HER in potentially lifesaving circumstances and liberals who have already been waiting more than a year for the planning and implementation of the NIH guidelines.

The NIH guidelines could have been implemented in June 2001. The wheels of government move slowly. Merging the change in policy by the Bush administration with the NIH guidelines, as well as the scrutiny that must be given to each cell line proposed for NIH funding, will require many more months of waiting. The toll of further delay is loss of opportunity to gain the answers needed for human trials and the inferences that follow for possibly avoidable human suffering and death. Which sources of stem cells will be best to treat dis-

eases safely and effectively? The NIH peer review process will lead to the most truthful answer to this question, but it will be many more months in the making. The NIH guidelines would have assured an ample supply of ESCs for research to answer the question. It is still unclear whether the Bush policy is based on an accurate assessment of the supply of ESCs. The entire process of discovery has been, in effect, set back by the Bush policy. In moral perspective, the Bush policy requires rigorous conservatives to compromise their basic principles, but it is insufficient to earn the status of a compassionate compromise.

The Bush policy is a compromise insofar as it breaks with the strictly absolutist position to prohibit all research on cell lines of ESCs derived from embryos. However, it is not a compassionate compromise because it dismantles the federal infrastructure for funding ESC research that had required almost two years to shape, and blocks access to ESCs derived (by industry) from frozen embryos after an arbitrary date of August 9, 2001. The NIH guidelines did not permit federal funds to be used to derive (and destroy) embryos to obtain stem cells; these acts were to be industry-supported activities. If it is morally acceptable for federal funds to be used to fund research on cell lines so obtained before August 9, 2001, why would it not be morally acceptable to continue a policy of walling off federal funds from derivation activities but permitting "downstream" research to be supported by an NIH that was fully prepared to do so six months after Bush became president? His willingness to permit research on cell lines already in existence shows that he could compromise an absolutist position on the degree of protection that society owes to embryos. By permitting federal support of ESC-related research, he placed a higher priority on helping seek cures for disease than he did on avoiding moral blame for linkage to destruction of embryos. Having breached this wall, he then drew back and covered it with an inference that had he been president at the time the NIH guidelines were proposed, he would not have allowed any research at all on ESCs derived from embryos. Then, rather than drawing the moral line at a rational place (i.e., no federal funds for the destruction of embryos), he drew it arbitrarily (i.e., on the basis of one religious view of the sanctity of the lives of embryos and a public policy that the earliest forms of human life deserve absolute societal protection). Surely, such is the president's view, which he stated during the campaign. However, this view ignores the great diversity, even within the same religious bodies, on the moral status of embryos.

What Bush has done is to enact a conservative social experiment which assumes that the supply of ESCs before August 9, 2001, is sufficient to answer es-

sential questions about ESCs, including whether their use can be bypassed by ASCs. If the supply is insufficient or the quality of the cell lines so impaired as to be useless, he will come under great pressure to redraw the line at a place where many more Americans and a more diverse religious community can understand (i.e., at a distinction between private and public support of destroying embryos but not allowing one religious view to restrict the pace of discovery and the potential for loss of life and increased suffering that accompanies it). The essence of compassionate compromise in this decision would have been to permit the NIH guidelines to stand and to allow the funding of ESC research into the future as a moral last resort and when there are "no less morally problematic alternatives available for advancing the research."[34] I cite the NBAC report here to show how it also came up to the point of compromise but then veered away to satisfy an aim to amend the ban on federal support for HER. My fuller analysis of the NBAC's moral reasoning will be published elsewhere.[35]

## The Need for Moral Compromise

The argument for "last resort" aims to reduce the degree of moral offense of HER to conservatives. In the context of debate about federal funding of derivation of ESCs, this could be done by timing the proposal to amend the ban with solid evidence that ESC research is the best avenue to hasten or increase clinical trials. My NBAC paper aimed to persuade the commission to this view. I was encouraged by a distinguished commissioner's statement of this position.[36] NBAC accepted some of my arguments, but decided without dissent to recommend that Congress amend the ban to enhance the scientific quality of the field, to encourage competition among scientists, and to bring federal controls to bear on the sources of stem cells. If the NIH funded derivation only from excess embryos, it could prohibit its grantees from doing research with cells from embryos created for research only or embryos created by cloning technology. These reasons are rational and plausible, but they do not take into account the depth of the opposition to HER among many conservatives.

In reflecting on why the opposition to the HERP's report was so strong, I identified three needs that shaped my argument for moral compromise on federal funding for ESC research. The first need is for patience born of understanding that moral evolution is a long and complex process. Embryo research is a major step in moral evolution. Moral beliefs about the human embryo

affirm its use for reproduction but not research. Why else would scientifically informed leaders like President Clinton and editorialists at the *Washington Post*[37] balk at the concept of generating embryos for science and not for reproduction? In pondering this question, I reread the partial dissent of Patricia King, a member of the HERP. King approved in principle the HERP recommendation for federal funding of research involving excess embryos. Her opposition to creating embryos for research was based on her reading of society's lack of preparation for this step. She wrote, "I do not believe that this society has developed the conceptual frameworks necessary to guide us down this slope."[38]

King's insight fits with James Rachels's fine analysis of the moral implications of Darwinism.[39] Rachels describes the slow pace with which moral traditions and institutions have come to terms with Darwin's discovery of evolution by natural selection. More than a hundred years after Darwin, major segments of our society still maintain that they are not descended from animals. Moral evolution takes a great deal of time and necessary conflict. In this light, moral revulsion over creating embryos for research ought to be understood as points on the map of moral and cultural evolution. There is a very long road ahead, and King was proven right by the response to the HERP report. In open democracies, an electorate and a judiciary informed by a variety of moral traditions help to guide the scope and pace of moral evolution. Patience with the pace of change in this arena is a public virtue. Liberals like me, who become pragmatists in ethics and politics, must learn to practice this virtue.

The second need is for compassion for the moral suffering of those who oppose embryo research but also hope for treatment of the sick and dying that could come from stem cell research. Persons suffer morally when they are caught between two right and good causes (i.e., affirmation of the intrinsic value of human life and for the cause of healing human diseases). In this regard, I was impressed with the writings of Alta Charo, also a member of HERP. She criticized the moral view in the HERP report that embryos have only "symbolic value" because it was dismissive of the moral concerns of those who believe that embryos are moral persons. She was also critical of the panel's moral reasoning as too "bioethical" because it focused almost exclusively on issues of moral status rather than on political ethics and on justice issues in particular.[40] Charo recently gave a mixed response to the Bush policy that is in essential agreement with the direction of this chapter.[41]

Taking Charo's argument seriously gives rise to a third need for a political

compromise on public support of HER. Is there a compromise that moderate conservatives and liberals can both support? It is only fair to the millions of Americans who already have cell-wasting diseases that public funds be invested in stem cell research, including promising work involving embryos. However, in striving for compassion and fairness, one ought to give as little moral offense as possible. This can be accomplished in the short run in three ways discussed in the next section.

## Reducing the Degree of Moral Offense in Stem Cell Research

There are three ways at present to reduce the degree of moral offense to opponents of using embryos in stem cell research: (1) to implement the proposed NIH guidelines for funding uses but not derivation of ESCs, (2) to impose conditions on amending the ban on federal support for HER, and (3) to pursue scientific alternatives to ESCs as sources of stem cells. Each of these approaches merits some discussion. In case of serious underestimation of the supply of ESCs for research after some initial success, the Bush administration could fall back on the NIH guidelines as an alternative policy.

### *Proposed NIH Guidelines*

The NIH's guidelines, which have now been overshadowed by the Bush decisions, were premised on an argument that funding the uses of ESCs in research is legally separable from the prohibition on funding derivation of ESCs, which destroys embryos in the process. Harriet Rabb, legal counsel to the Department of Health and Human Services (DHHS), shaped this position, arguing that ESCs cannot become embryos or a "living organism."[42] This position permits NIH funding of research uses of ESCs "downstream" from derivation supported by private funds. I view this option as a legal and political compromise about uses of federal funds to advance the field that avoids using taxpayer funds for destruction of embryos. As the ban covers only federal activities in science, private industry can legally fund derivation of ESCs in any state with no law that prohibits embryo research.

More than a year later (and only after its FY 2000 budget was approved), NIH published proposed guidelines to fund uses (but not derivation) of ESCs only from "excess" embryos.[43] NIH was poised to establish a Human Pluripotential Stem Cell Review Group to document compliance with the guidelines and hold public review meetings on proposals to fund uses of cell lines derived

with support of private industry from donated embryos or fetal tissue. The NIH proposal had important support from Senators Arlen Specter (R-PA) and Strom Thurmond (R-SC), who are conservatives. Senator Orrin Hatch (R-UT) also subsequently expressed support for this position. Jay Dickey (R-AK) and Henry Hyde (R-IL) oppose NIH's proposal and aim to block it in court.[44] Twenty senators, including former presidential candidate John McCain,[45] signed a letter of opposition. The political situation on this issue is less volatile following the Bush decision. However, the NIH proposal represented the best hope in the short run for genuine political and moral compromise. Public funds would not be used for derivation, but NIH peer review and support would be available for important studies of the properties of stem cells derived from different sources. Both liberals and many moderate conservatives could support this step without amending the ban.

During the NBAC's debate on ES cell research, the arguments of a few members reflected a desire to compromise on the issue of federal funding.[46] If a minority had emerged and dissented, its position would have been similar to a report of an advisory group[47] to the AAAS and the Institute for Civil Society (ICS), which supported the NIH proposal.

The rate of progress to trials of cell-replacement therapy is a political and an ethical issue. If this form of treatment is proven to be safe and effective, a difference of either five or ten years to the implementation of therapy will impact millions of people and their families. NIH funding of both derivation and use of ESCs will probably speed progress, as argued by NBAC. NBAC argued for federal support of research with all sources of stem cells, except with embryos created for the sake of research or made by cloning technology, and it recommended that Congress amend the ban.[48]

### *Conditions for Amending the Ban*

At times political reality can disrupt an ideal goal. Given the troubled history of Congress concerning fetal and embryo research, one can expect protracted conflict over ESC research. Conflict could even undermine the minimalist Bush position and the moderate NIH position. My thesis is that the stance that supports federal funding of ESC research as a "last resort" to bridge between successful animal experiments and human trials using ESCs has a far greater chance of political success than the NBAC position. NBAC argued that Congress ought to amend the ban now. There will be less moral offense and more conservative votes, however, if some basic scientific questions have been

answered with funding by private industry in tandem with the NIH's planned approach. If supply of ESCs is not a serious problem, the same result could occur under the Bush plan. The argument combines projections about the future of stem cell research and considerations of distributive justice.

Two types of experiments are currently preceding clinical trials of cell-replacement therapy: (a) basic research and (b) preclinical research involving the study of ES, EG, and adult stem cells (ASCs) in animal models for human diseases. Scientists are now doing these two types of research concurrently, although the first small clinical trials using ASC-derived cells are beginning.

### Basic Research

These activities involve studies of techniques of derivation, properties of cell lines grown from different sources of human stem cells, and learning to guide differentiation of specific cell lines.[49] Dr. Brigid Hogan[50] noted differences in DNA modification between mouse EGCs and ESCs. The differences may be due to methylation, a process that protects recognition sites of DNA and plays a regulatory role in gene expression. Cells derived from EGs may have less methylation than normal. The scientific and (possible) clinical import of these differences needs exploration. Dr. Hogan emphasized the need for access to both types of cells for this purpose.[51] In a recent article she also emphasized how little is known about the origin of ESCs.[52] The properties of ASCs and their potential are the subject of intense study. Clarke et al. recently reported that when neural stem cells from the mouse were injected into mouse and chick embryos, they gave rise to many types of cells of all germ layers.[53] This experiment shows that ASC cells may have the same capacity and flexibility as ESC cells. When the latter are injected into mouse embryos, they contribute to all of the tissues in the subsequent chimeric mouse. The findings of Clarke et al. will need to be replicated by other studies, but raise hopes that ASCs will prove to be viable sources of cell lines for therapy.

### Preclinical Research

Concurrently, investigators are doing experiments with animals and with human stem cells in the laboratory. These studies need to go beyond the proof of concept and include extensive examination of potential toxicities as well as chronic versus acute effects. It will be mandatory, before human trials, to show that purified cell lines derived from ESCs or other sources are not tumorigenic in mice or other animals. Preclinical research aims at consensus about the sci-

entific feasibility and moral justification of human trials for one or more candidate diseases. Some of the most important studies of this type are discussed in a section below on alternatives to ESCs.

Clinical Trials

If a consensus can be reached on preclinical and ethical readiness for trials, a series of clinical trials in humans of investigational cell-replacement therapies will follow. These studies will aim to answer this question: Is cell-replacement therapy safe and effective in human beings? These trials will be done under Food and Drug Administration regulations as an investigational new drug (IND) application. Early phase I trials of cell-replacement therapy using ASC-derived cell lines have begun, as also discussed below.

The claims of distributive justice bear directly on two issues in stem cell research. The first issue is fairness in use of public funds to hasten clinical trials. It is unfair to the more than one million Americans[54] who have illnesses that might be treated by cell replacement, and who are also taxpayers, to maintain a ban that slows progress to human trials.

Federal support following the NIH guidelines, rather than the Bush policy, could mean a transition to trials of some four to six years rather than eight to ten years. The ethical question is whether any delay, even to gain evidence to justify amending the ban, is justifiable. Let us assume for purpose of argument that NBAC's position is right that the ban be amended to permit federal support. Even so, political opposition to rescinding the ban, bolstered by lack of evidence about the comparative merits of ESC research, could block such action indefinitely. At this time, there is not a clear majority in Congress to amend the ban. In this context, the time is ripe for compromise, if Congress can muster the political will to move faster than the Bush policy will allow.

To defer amending the ban for the sake of compromise will seem unfair to a liberal assessment of justice issues, the moral status of embryos, and the need for federal funding. However, a delay to show respect for conservatives' moral views and to appeal for an exception to the ban to hasten therapeutic trials has a chance of success. If the conditions in Table 8.1 were met, conservatives in Congress could vote to amend the ban with assurance that "no less morally problematic alternatives are available for advancing the research." The NBAC report used the language of last resort but did not adhere to it in its recommendations on federal funding.[55] To amend the ban after the conditions in Table 8.1 have been met is a better fit with the moral logic of "no less morally

*Table 8.1. Conditions for Federal Funding of ES Cell Research*

1. NIH "downstream" and private industry support of research leads to understanding of cell differentiation and differences between ES, EG, and AS cells.
2. Scientists successfully conduct experiments in animal models with ESCs and show that tumorigenic dangers and other potential hazards of using ESCs can be avoided.
3. Scientists agree that preclinical data justify clinical trials for one or more diseases that are life threatening or severely debilitating, because of the particular promise of ESCs as sources of cell lines to treat those diseases.
4. Scientists agree that derivation of ESCs is required as a "last resort" to grow cell lines for such trials because alternative sources of stem cells will probably not work as well.
5. Grantees and contractors assure that (a) IRB approval has been obtained for a two-stage consent process that separates infertility treatment decisions from decisions to donate embryos for research and a plan to protect the privacy of donors, (b) such research with donated embryos will conform to guidelines recommended by NBAC and NIH, and (c) fairness in selection of subjects to donate excess embryos will be assured.
6. Funding for stem cell research includes a process to ensure fairness in selection of subjects in clinical trials of cell-replacement therapy.*

*The FDA and the NIH have increasingly mandated equity in access to clinical trials, notably to require gender equality and (in the case of the FDA) to redefine pediatric labeling and study requirements. FDA/NIH could be meaningful partners in applying access requirements equally to both publicly and privately funded studies.

problematic alternatives." This way gives the least offense to conservative moral views and is morally balanced by liberals having to compromise their position that the ban was in "conflict with several of the ethical goals of medicine, especially healing, prevention, and research."[56]

The conditions listed in Table 8.1 are foreseeable within two to three years after NIH funding of uses of ESCs. These conditions will be sufficient to move moderate conservatives to amend the ban. Their vote will be based on much more evidence that derivation of ESCs has a great potential to benefit the sick and disabled. More evidence is available today than the NBAC had in mid-1999 for its report. However, more evidence is needed than exists at present.

### *Alternatives to Embryonic Stem Cells*

One of the most important scientific and ethical questions in stem cell research is whether there are viable alternatives to the need for ESCs. This question cannot be answered without more research, especially of the kind that compares the properties and potential of the several sources of stem cells and cell lines. At present, the question focuses largely on the properties and poten-

tial of ASCs, which are derived from the human body and raise no moral concerns other than the level of safety required to obtain them.

There are many more published reports of research successes in mice using various types of ASCs than ESCs or EGs. Vogel[57] discussed a spate of ASC experiments in a *Science* article featuring stem cell research as the "breakthrough of the year." As the Dolly cloning experiment showed,[58] AS cells have the remarkable power to revert to their embryonic state and grow new cells. AS neural cells can also be dedifferentiated to become blood cells.[59] Vogel wrote: "signals in the immediate environment can in some cases override a cell's history, implying that nature allows developing cells far more freedom than scientists had imagined."[60] Research in mice is confirming this concept. For example, Jackson et al. induced cells derived from skeletal muscle to become blood cells and successfully engrafted irradiated recipients.[61] Investigators also demonstrated in mouse models that muscular dystrophy[62] and diseases of the central nervous system[63] might be treated by neural stem cell transplants. Ourednik et al.[64] expertly reviewed the prospects for treatment of diseases of the central nervous system by use of neural stem cells, perhaps combined with gene therapy.

It appears that preclinical research in animals involving ESCs will also provide models for human trials. A dramatic experiment by McDonald and colleagues used ESC-derived nerve cells to restore partial spinal cord function in paralyzed rats.[65] Vogel also reported in a recent article that several other centers have done promising work in animals using ESC-derived cell lines.[66] She also discussed what scientists perceive to be the pros and cons of ASCs and ESCs. ASCs may be easier to manage because ESCs "tend to differentiate spontaneously into all kinds of tissue" (1419). However, ASCs may have a shorter life span than ESCs that would make them less effective for some medical uses. It remains to be seen what weight these differences carry in the future and whether ESCs can be guided to develop into *only* the desired cell line or tissue. The moral advantages of using AS cells are clear, but the scientific issues cannot be settled without much more evidence. Progress is being made in animal studies of ESCs. For example, researchers at the NIH recently discovered a way to make insulin-producing cells from mouse ESCs, and the experiment will be replicated using human ESCs in the laboratory at Harvard University.[67]

Phase I trials in humans using ASCs have begun. A phase I clinical trial using mesenchymal stem cells for allogenic bone marrow transplants was done in three children with osteogenesis imperfecta.[68] There were increases in new

bone growth and prevention of fractures. Unless animal research shows that it would be unsafe, clinical trials with stem cells derived from each source should be anticipated. Meanwhile, a race is on among companies that largely specialize in growing ASCs for research, especially for treatment of neurodegenerative diseases.[69] Comparative evidence about the potential of each source of cell lines will gradually accumulate so that members of Congress will know whether amending the ban to permit funding of HER is clearly in the interest of saving lives. Liberal supporters of HER need to cultivate the patience to wait until the evidence is available. The better road to amending the ban, if it is necessary, is to wait until the data show that human trials of cell-replacement therapy for some or any disease cannot be optimally done without deriving ESCs for that experiment. At that point and with sufficient data in hand, members of Congress can be confident that they can defend their vote as one aimed to save lives and prevent disability.

## Intersections with Gene Transfer and IGM

Discussion of scientific and moral aspects of stem cell research intersects with the topics of gene transfer experiments and IGM in humans. Stem cells may have potent uses in research on human gene transfer in the hope of treating genetic disorders. Will stem cell–assisted gene transfer resolve major technical problems in using exogenous vectors to introduce corrective DNA to target sites? Dr. Austin Smith's testimony to NBAC[70] and an NIH discussion paper on cloning point in this direction.[71] Pincus et al.[72] discuss the use of neural stem cells that persist in the adult brain as a vector to performing gene therapy in neurodegenerative diseases. Their review cites a successful neonatal experiment in a mouse model for mucopolysaccharidosis.[73]

Uses of stem cells in the context of human somatic cell gene transfer raise no new ethical questions. However, any use of stem cells in tandem with the intent of IGM in the DNA of gametes or preimplantation embryos raises a host of old and new issues. Dr. Erik Parens's testimony to NBAC notes how stem cell research will converge into experiments to treat the DNA of human embryos and prevent genetic diseases in children-to-be.[74] His commissioned paper for NBAC[75] explores this linkage in more detail. He points out that it is easier to make corrections in DNA in stem cells derived from embryos than in zygotes or somatic cells. After such genetic alteration, these cells could be fused with a blastocyst to give rise to an embryo "derived solely from the ESCs, and that em-

bryo can give rise to a genetically altered organism." A great deal of research remains to be done before the achievement of such a goal, but it is predictable that stem cell research will eventually converge with IGM. The NBAC report did not examine the interface between stem cell research and IGM. This task remains to be done.

## From Animal to Gamete to Embryo

In prior writings,[76] I defended HER as an acceptable means to understand whether harmful mutations could be corrected at the earliest stage of embryonic development. In this vein, my first paper for the AAAS working group envisioned an experiment with affected embryos that required two phases. In the first phase, IGM would be attempted by gene targeting soon after in vitro fertilization. However, no transfer to the uterus would occur. Study of the blastocyst's cells would occur to ascertain correction of the DNA at eleven to twelve days after fertilization, when there are approximately a hundred cells. The study could be stopped before the appearance of the primitive streak. This outer limit for HER was recommended by the Warnock Committee in the United Kingdom[77] and by the NIH Human Embryo Research Panel.[78]

If the harmful mutations in the first blastocyst's DNA were corrected, the experiment would move to a second phase, where the entire experiment could then be repeated with a higher standard of safety. The second treated blastocyst could be transferred at an earlier stage to the Fallopian tube for implantation in the uterus. Without a phase I to demonstrate feasibility and safety, there could be higher risk of an avoidable "mistake" with harmful consequences, including transmission to future offspring. If a primary ethical concern is to avoid humanly created mistakes in the genome of the treated individual, one ought to be as confident as possible that the original intervention was effective (i.e., the mutation has been altered in the embryo as desired).

My view on the need for such an experiment changed during the AAAS project due to the implications of Chapter 6 in this volume on gene repair mechanisms that avoid viral or other vectors. In it, Dr. Culver describes oligonucleotide gene repair technologies, including his own work with third-strand-forming bifunctional oligonucleotides.[79] Two other approaches to gene repair are small fragment homologous replacement and RNA-DNA chimeric oligonucleotides. The noteworthy characteristic of these approaches is that they do

not insert viral vectors into the target DNA and the oligonucleotides are degraded within hours. These technologies are still in early development and may indeed not work out. However, the recommendations of the working group are based on the condition that there must be gene technologies in the future that will correct the mutation by returning it to the wild type. The working group considered it too hazardous to use conventional methods of gene transfer in the context of intentional IGM.

If research with such approaches to gene repair succeed in animal models, then the morally optimal site for the first experiments of IGM in humans is with gametes or their precursors. The first experiments ought to be aimed at correcting mutations causing azoospermia or disorders of oogenesis that lead to infertility. Further, the DNA repair mechanism should not introduce exogenous DNA into the genome, as would a viral vector. The repair should do no more than return the DNA sequence to the wild type, which is the type arbitrarily presumed to be normal. The morally optimal sequence of experiments in IGM is from animal to gamete to embryo. If DNA repair with gametes or embryos proved safe in animal models with the same genetic mutations as humans, then the work could be safely extended to human gametes. Any IGM experiments with human embryos would be indicated only for genetic disorders that could not be corrected in gametes. These could include disorders due to genetic imprinting, a process that occurs after fertilization and frequently results in pediatric cancer.

Basic questions in animal research must be answered before any experiments with IGM in human gametes or embryos could be morally defended. Can IGMs be induced in animal models engineered to have the same harmful mutations that human beings also inherit? Will the repaired DNA in these "humanlike" animals be transmitted to offspring who grow and develop normally? Will these offspring reproduce without transmitting the original harmful mutation? Will they and their offspring have no higher risk of cancer or suffer unforeseen side effects?

If these questions can be answered affirmatively, a scientific foundation for experiments with IGM in human gametes will have been laid. At that point in history, the potential of human IGM and the issue of the necessity of HER can finally be addressed. If new genetic technologies failed to correct mutations in gametes, then my views would be open to attempts to correct these mutations in embryos as a last resort for IGM.

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CHAPTER NINE

# The Implications of Inheritable Genetic Modifications for Justice

Audrey R. Chapman, Ph.D.

Analysts, characterizing human genetics as the "preeminent science of inequality,"[1] have raised concerns that the benefits and burdens of the genetic revolution will be unequally and unfairly distributed. This literature, much of it dating from the early 1990s, considers the Human Genome Project, genetic testing, reproductive decisions, genetic discrimination, and, to a lesser extent, gene therapy. In almost all cases, gene therapy is equated with somatic modifications. Much less has been published specifically considering inheritable genetic modifications (IGM). This chapter considers potential efforts to undertake human genetic modifications across generations both to eliminate disease-related genes and to enhance or improve human characteristics and their implications for justice.

Before beginning the analysis, I would like to acknowledge that an assessment of a new technology well in advance of its development (in the case of IGM it will likely be decades before a range of applications can responsibly be applied to human subjects) is obviously a speculative enterprise. The impact of IGM, if and when it becomes a clinical option, will depend on a wide variety of factors. These include the nature of the health care system, the type of health

insurance available and the population covered, public policies regulating genetic and reproductive technologies, social attitudes toward a variety of matters relating to genetics, and the degree of commitment to social equity. Complicating matters still further, as the genetic revolution proceeds, the knowledge and technologies it generates doubtlessly will interact with and influence the health system, public policy, and attitudes regarding a wide variety of health-related matters. Moreover, a new age of genetic intervention may also reshape some of our thinking about the requirements of justice, especially in relationship to genetic services.[2]

Nevertheless, given the potential import of this technology, it is important to assess IGM well in advance of its availability and to encourage meaningful public discussion of the implications for justice it raises. There are two different sets of issues that require attention: first, whether proceeding with IGM will aggravate and complicate the various issues that other genetic developments already raise, and second, whether germ-line modifications will introduce new problematic factors into the justice equation. Those who aspire to create a more just society also need to evaluate how serious these issues are, and whether any constitute a sufficient societal challenge to warrant recommending against proceeding with such interventions. If a societal decision is made to go forward, or more likely no measures are adopted to prevent the private sector from doing so, anticipating the inequities and inequalities that will ensue from IGM can also prepare policy makers to undertake corrective measures.

## Concepts of Justice Relevant to IGM

Justice is a multifaceted and complex concept, and theorists differ in their approaches to it. Most treatments, however, concur that justice, at a minimum, requires fair, equitable, and appropriate treatment in light of what is due or owed to persons. Conversely, a wrongful act or omission that denies an individual or a group the benefits to which the person or group has a rightful claim, or alternatively fails to distribute burdens in a fair manner, constitutes a form of injustice. Justice has social as well as individual dimensions. *Distributive justice,* the type of justice most relevant to the issues raised in this essay, refers to the morally justifiable distributions of benefits and burdens in a society as defined by the norms that structure the terms of social cooperation.[3] To determine what is fair and appropriate, many writers refer to the formal principle of justice, usually attributed to Aristotle: treat equals equally; treat unequals

unequally.[4] This formal schema, however, lacks content—that is, the specification of the criteria to be used to make these determinations.

Philosophers have therefore proposed a variety of material principles or bases to assess what constitutes the equitable and appropriate distribution of benefits and burdens in a society. Those most frequently cited material principles include:

- equality: benefits and burdens should be distributed equally
- need: benefits and burdens should be distributed according to need
- merit: benefits and burdens should be distributed according to merit and achievement
- utility: benefits and burdens should be distributed according to a policy that produces the greatest balance of benefits over burdens for all members of society
- free choice: benefits and burdens should be distributed according to the choices people make when rights are not violated[5]
- free-market exchanges: benefits and burdens should be determined according to free-market exchanges[6]

Theories and treatments of justice differ regarding which of the material principles should govern the fair distribution of benefits and burdens. Two of the most frequently cited are an egalitarian approach to justice based on equality and need and a libertarian approach emphasizing liberty and the unfettered operation of the market. Because of these very different understandings of justice, analysts often disagree not so much about the likely scenario of what may unfold as a consequence of going forward with IGM, but about evaluating its implications. As an example, ethicists may agree that permitting privately funded human germ-line applications would likely significantly increase inequality within society. Those holding an egalitarian or needs-based approach to just distributions would understandably find such a scenario problematic, particularly if the unequal outcomes resulted from inequalities in access to technology. In contrast, those thinkers emphasizing a free choice or market-based approach to justice would be less disturbed. Instead, their reaction likely would be to contend that growing inequalities are an acceptable outcome of preserving the right of couples to unlimited free choices of reproductive options or the right of private investors to develop and offer any profit-making reproductive services.[7]

My view, which is closest to an egalitarian or needs-based approach to jus-

tice, is predicated on the obligation to provide core health services to all members of society. As someone with a background working on health and human rights issues, I have long believed that every state should recognize a right to a basic and adequate standard of health protection and care consistent with its level of resources.[8] Major human rights instruments, including the Universal Declaration of Human Rights, state that all persons are entitled to basic economic and social rights, among them a right to health protection and health care.[9] Key philosophers, ethicists, and religious thinkers also affirm the centrality of health for preserving life's options. Perhaps the best known is the philosopher Norman Daniels, who argues that health care constitutes one of society's primary means for providing "fair equality of opportunity" for its citizens through services and interventions that counter the natural disadvantages to physical, sensory, or cognitive functioning imposed by disease.[10] Other thinkers go further to claim that a just health care system must be based on a vision of the common good, rather than favoring specific groups or interests.[11] In most democratic political systems in industrialized countries (other than the United States), health care is considered to be a fundamentally important social good that should be distributed according to egalitarian and not free market or libertarian conceptions of justice.[12] In those countries, access to an adequate standard of health care is guaranteed to all citizens and residents, and the financing of basic health care services is a public responsibility. Therefore, the quality and availability of at least basic health services does not depend on an individual's financial resources.[13]

## Distributive Justice: The Issue of Societal Investments

Problems of distributive justice typically arise under conditions of scarcity and competition, when resources are insufficient or trade-offs are required. This certainly characterizes the situation for prospective germ-line technologies. IGM will require very considerable resource investments from the public and private sectors over a long period of time, particularly if scientists are to develop new forms of genetic technology so as to make clinical applications safe and effective. There are three potential scenarios. If IGM is developed with public funds so as to assure proper regulatory oversight, the resources invested in IGM will most likely come at the expense of other social investments, including research to produce other types of medical innovations. Alternatively, if IGM is developed by the private sector, like other privately funded high-tech-

nology innovations (e.g., somatic cell genetic therapy), it will probably be very expensive. This will raise significant access issues. Corporate investment will also skew development in favor of the most profitable rather than the most beneficial forms of germ-line therapy. (On this point, see Chapter 19 in this volume.) Finally, if germ-line technologies emerge from a public-private partnership, neither set of disadvantages—the burdens of public investment or the limitations of access—may be resolved.

Would a major public investment in germ-line technologies be wise, fair, or equitable from a societal perspective? Scientists have discovered a strong genetic basis or component for over 6,000 diseases,[14] many of which cause serious health problems and significant disability. One of the major arguments for developing IGM is that it can provide an efficient means of preventing, even eliminating, some genetically based diseases. However, virtually all investments in genetic science have been justified as a potential contribution to improving human health and relieving suffering. In the early stages of its development, human gene therapy was heralded as "a symbol of hope in a vast sea of human suffering due to heredity."[15] Despite this considerable hype, gene therapy has not fulfilled its promise. Thus far the major contribution of genetic science has been to diagnose rather than to treat genetically based disorders. While some patients have been helped and a few cured, the overwhelming majority of the several thousand patients who have enrolled in gene therapy trials have not received any benefit.[16]

Moreover, IGM would be a very high-risk public investment. Some advocates argue that "the real question about germ-line engineering is not whether the technology will become feasible, but when and how it will."[17] But IGM is a more ambitious and complex undertaking than any medical technology yet developed. Given the need for scientists to develop fundamentally new technologies and approaches so as to meet the stringent safety and efficacy standards required for multigenerational genetic interventions, there are ample grounds to be cautious about the prospects for engaging in responsible human IGM. There are also serious hurdles involved in developing a means to test and evaluate the safety and efficacy of germ-line procedures across several generations before beginning human trials. Moreover, even if IGM were to become technically feasible, it will not necessarily receive regulatory, social, or ethical approval.

Another relevant distributive justice issue is the investment-benefit ratio: if requisite public financial investments were to be made and IGM were to become a reality, would the number of people who might potentially be benefited,

particularly those who would otherwise lack alternatives, warrant the very considerable costs? The pharmaceutical industry frequently claims that it takes several hundred million dollars and a decade of work to bring a new drug from the laboratory to the clinic, and IGM is a far more ambitious undertaking than the development of a new drug. IGM would likely require many billions of dollars for research and development. Further, there would be the costs of the genetic and developmental mistakes in the form of people with mental, physical, or emotional dysfunction inadvertently resulting from germ-line treatments. To argue that individuals have the right to shape the genetic heritage of their offspring, even to take risks of harming them, ignores the fact that those who will suffer these adverse outcomes will be born in the future, possibly several generations in the future, and their problems will become the moral and financial responsibility of others. One team of analysts anticipates that the economic costs of taking care of people who are born with such "human-made" genetic diseases and disabilities is likely to outweigh the economic benefits obtained from preventing genetic diseases.[18] And this balance sheet does not even begin to take into account the ethical and social costs that IGM would entail.

Therefore, it is important to assess how many people could receive therapeutic benefits from this very costly investment who would otherwise lack treatment alternatives. The answer is very few, certainly not a sufficient number to justify the enormous financial resources IGM would require. Importantly, the working group convened by the American Association for the Advancement of Science (AAAS) identified few scenarios where there were no alternatives to IGM for couples to minimize the prospect of passing on defective genes to offspring. In vitro fertilization combined with preimplantation diagnosis and selection of zygotes offers one potential reproductive option. Prenatal diagnosis and therapeutic abortion is another possibility for attempting to eliminate many genetic abnormalities. Improvements in somatic gene therapy, particularly if it becomes feasible to proceed with in utero treatment, may offer yet another approach. IGM would be far more complicated and impose greater safety risks than any of these. Moreover, at least initially, germ-line transfers would still require prenatal diagnosis "just in case," with the prospect of selective abortions to avoid "mistakes." Therefore, IGM would not offer a way around the problems that pro-life advocates have with preimplantation diagnosis and selective discarding of embryos.

The AAAS working group could identify only two potential therapeutic applications of IGM where there are no other treatments or options currently

available. The first was a situation where both parents are homozygous for a monogenic defect and are desirous of having a genetically related child. Embryo selection would not be a viable alternative since neither parent would have a normal allele. Gamete donation could, however, provide an option for such couples. The second potential application was to treat some forms of male infertility by modifying sperm or spermatogonia, the stem cell precursor of fully matured spermatocytes. (See Chapter 6 in this volume for further discussion of this application.) While this could potentially benefit larger numbers of people, there are already alternative ways, such as intracytoplasmic sperm injection (ICSI), for treating infertility in the male so as to produce a genetically related child. It is also very questionable whether conferring the ability for a relatively small number of couples to have a genetically related child is worth the social costs and investments outlined above; I certainly do not think that it is. Other analysts have reached similar conclusions that there are few therapeutic targets requiring germ-line interventions.[19] Thus the major driver for IGM, particularly for private-sector investments, is likely to be its potential use for enhancing characteristics and traits.

Finally, it needs to be emphasized that there are other types of health investments that are far more likely to contribute to public health and welfare. Despite the fact that the United States has the highest per capita health expenditures in the world, Census Bureau figures indicate that the number of Americans without health insurance rose to 41.2 million in 2001, an increase of 1.4 million people.[20] This means that 14.6 percent of the population lacked health insurance, and many other persons had insurance with insufficient coverage.[21] As these trends indicate, in a serious economic downturn many more people are vulnerable to losing their jobs and their health coverage along with them. The lack of health insurance often results in inadequate health care, particularly if the illness or disability requires something more than an occasional consultation with a doctor.[22] But as health care needs grow, the decline in the revenues of the federal and state governments make it difficult for them to increase their aid. Clearly, the most pressing national health priority in this country is guaranteeing universal access to basic health care and not developing more high-technology medical interventions needed by a relatively small number of people. And various preventive health measures, such as cleaning up the environment in order to reduce exposure to toxic substances, would also be a more effective societal health investment.

## Access to Genetic Therapies

Anticipation of problems in assuring equity in access to the benefits of genetic therapies to prevent and treat genetic disorders has been a recurrent theme in the literature on genetics. This situation reflects a number of factors in this country: the lack of a system of universal health insurance, patterns of inequalities in access to health care, a projected scarcity in the availability of genetic services relative to demand, and the likely high cost of such interventions. Access will undoubtedly also be limited by the need for considerable knowledge and sophistication to take advantage of such a complex technology.

Problems in obtaining access to health care are unfairly distributed throughout our society. The coverage gap particularly affects the poor and ethnic and racial minorities. This disparity is generally attributed to lower incomes, the type of employment available, and the absence of doctors and medical facilities in their areas of residence. Most of those without health insurance are working in low-paying or temporary jobs and do not have either health care benefits or the means to pay the rising employee contributions required by employers. In 2001 half of poor people working full-time were uninsured as compared with 16 percent of all full-time workers.[23] According to Census Bureau figures, 10 percent of whites lacked health insurance for all of 2001, compared to 19 percent of blacks, 18 percent of Asians, and 33 percent of Hispanics.[24] Various studies have also shown that minorities with insurance are more likely to have only minimal or basic coverage.[25]

A configuration of factors that might be termed "therapeutic discrimination" also affects the health care that minorities receive. A very disturbing report issued by the Institute of Medicine in 2002 concludes that racial and ethnic minorities in the United States receive notably lower-quality health care, even when they have the same incomes, insurance coverage, and medical conditions as whites. The study, based on a review of a hundred studies conducted during the previous decade, shows that these differentials are particularly significant for high-technology care and interventions. Members of minorities are less likely to receive organ transplants, bypass surgery, the best diagnostic tests and treatments for cancer, and the most sophisticated treatment for a range of diseases. Disparities in treatment then contribute to higher death rates for minorities than whites who are suffering from illnesses of comparable severity.

The report attributes these findings to subtle racial biases, the nature of facilities available in specific geographic areas, and lower rates of long-term relationships with treating physicians.[26]

Currently, approximately one-fourth of all health care benefits in the United States are being underwritten by either Medicare or Medicaid.[27] These programs primarily serve two groups: those who cannot afford their own health care, a disproportionate number of whom are members of minority groups, and the elderly. Given the increasing pressures to contain costs, policy makers are likely to continue to restrict the services that are covered under these programs or to constrain their availability.

IGMs will therefore most likely be available only to those with expensive private insurance or sufficient wealth to purchase them. At a minimum, most private insurance agencies may be inclined to delay underwriting the cost of genetic services until their efficacy and safety are clearly demonstrated. Another likely impediment to the accessibility of germ-line interventions is the reluctance of most health insurers to pay for high-technology reproductive services like in vitro fertilization. Both federal programs and private health insurance policies rarely cover anything considered to be nontherapeutic. This would of course apply to enhancement modifications. Further, because enhancement technologies will probably be developed within the private sector, they are likely to be even more expensive than somatic genetic therapies that currently cost several hundred thousand dollars per patient. This would virtually guarantee that genetic enhancements would be available only to a narrow, wealthy segment of society.

Could fundamental health care reform rectify the situation? The findings in the Institute of Medicine report suggest that even providing universal access to medical services, including IGM, would not translate into equality in the availability of treatment. Under a system of universal health care providing entitlements to some forms of genetic services—which is a very unlikely development in this country—the very groups who currently lack equal access to medical care would still be disadvantaged by many of the factors noted in the Institute of Medicine study. The implications will be discussed in subsequent sections of this chapter.

## Reinforce or Increase Existing Discrimination

Many ethicists have expressed concerns that the expansion in genetic knowledge and testing will reinforce prejudices and worsen discrimination based on

actual or presumed genetic differences. This is particularly a problem in a country like our own, which has a long and disturbing history of drawing sharp distinctions among citizens on the basis of race and ethnicity and where many persons harbor beliefs in biological determinism.

Members of the disabilities rights community also anticipate that the desire to improve the human condition through genetic and reproductive intervention will increase intolerance toward persons with disabilities, especially if these problems are genetically based. Sociologist Marque-Lisa Miringoff's book *The Social Costs of Genetic Welfare*[28] contrasts two sets of attitudes or dispositions toward persons with genetic diseases. The first, which she terms a social welfare view, seeks to reconstitute the environment through social welfare measures, laws, and policy in order to accommodate the special needs of persons with disabilities and thereby encourage greater inclusion and expanded opportunities. She contrasts this approach with a genetic vision seeking to excise or biologically refashion those with disabilities. Because such a "genetic welfare" perspective emphasizes biological fitness, one logical extension is to prevent such people from being born or procreating. Since her book was published in 1991 another biological option, somatic gene therapy, has become available, albeit for limited purposes and only recently with some success.[29] Miringoff contends that rapidly developing and scientifically alluring genetic technologies are spurring the adoption of a genetic welfare perspective. She points out some of the misplaced priorities that have resulted: while vast amounts of money are invested in genetic screening and reproductive techniques, mostly for middle- and upper-class women, we fail to invest in basic forms of health care. As a result, poor women give birth to underweight, undertreated, and chemically exposed babies, with similarly injurious forms of disease and retardation.[30]

There is already evidence that genetic discrimination is beginning to affect eligibility for employment and insurance. An increased ability to predict health risks, combined with a health insurance system in which employers bear most of the costs, provides incentives for employers to discriminate against individuals with genetic predispositions to diseases. Insurance companies have used genetic tests to identify "preexisting conditions," and then used this determination as grounds for denying claims or refusing coverage.[31] In 2001, the U.S. Equal Employment Opportunity Commission (EEOC) settled its first court action challenging the use of workplace genetic testing under the Americans with Disabilities Act of 1990.[32]

Another issue bears examination: the possibility that introducing IGM without undertaking the reform of our current health insurance system may impose further pressures not to bear children with genetic dispositions toward disease or disability. Insurers make considerable effort to selectively insure those most likely to remain relatively healthy. If germ-line intervention becomes feasible, insurers may demand that policy holders take additional measures to reduce the prospects that any children who are born during the life of the policy do not have genetic diseases. Prospective parents may have to undergo a battery of genetic tests and, if diagnosed with a genetic disorder, they may be required to agree to take measures to prevent the birth of a child with a genetic disorder. One likely measure would be to insist that all at-risk parents test any conceptus, and, if it is found to harbor problematic mutations, to either abort the pregnancy or undergo germ-line modification in order to retain family coverage.

At the least, the possibilities of engineering inheritable modifications are likely to tip the balance even further toward an inclination to resort to a technological fix of genetic assessments and interventions. Some social critics already claim we are moving in this direction. The Council for Responsible Genetics (CRG) argues that germ-line intervention, combined with a doctrine of social advancement through biological perfectibility, will mean that persons who fall short of some technically achievable ideal will increasingly be seen as "damaged goods." CRG also assumes that the standards for what is genetically desirable will be set by our society's economically and politically dominant groups.[33]

Others do not agree with CRG's assessment. Ted Peters, a moral theologian at the Center for Theology and the Natural Sciences who writes frequently on topics relating to genetics, takes issue with the assumption that germ-line intervention implies biological perfectibility. He also disagrees with the CRG's prognostication that germ-line modification will necessarily reinforce prejudice and discrimination. Nevertheless, he does acknowledge that there could be problems. One example he mentions would be a worldwide program to eliminate the predisposition to a particular disease from the human gene pool that achieved success in some ethnic or class groups, but then for financial or other reasons the government abandoned the project. In such a situation individuals who still carried the disposition might suffer increased stigma or discrimination.[34] And such selective interventions and uneven changes would likely be the outcome of differential access to this technology.

## Challenges to Equality

Equality of opportunity requires that a person's life prospects should depend on factors within his or her own control and the removal of social and political barriers. Some analysts warn that the genetic revolution will pose unprecedented challenges to equality, particularly in a society likely to have unequal access to genetic services, such as ours. Likely, it will also be far more problematic to affirm the meaningfulness of the principle of equality of opportunity when genetic evidence points to vast differences in natural endowments. While our "standard model" for thinking about equality of opportunity acknowledges the fact that talents and skills and other capabilities are not distributed equally among people, democratic societies generally try to limit the social and political implications of these differences through public policies. To ensure fair equality of opportunity, our policies require judging people by their capabilities while ignoring "morally irrelevant" traits, such as sex or race.[35] Another way is mitigating or compensating for some of the differences in the normal distribution of capabilities, such as giving students with learning disabilities more time to take examinations.

If we develop IGM, the problem will be even greater. Unequal access to germline technologies will also mean that those persons who can already provide the best "environments" for their children will also be able to purchase the best "natures." Because germ-line modifications will be cumulative, the advantages and enhancements of one generation will be passed on to their progeny. How much of an advantage this will confer and thereby contribute to inequality will depend, of course, on the types of modifications that will become possible and the public policies that regulate the scope of germ-line interventions and shape access.

Does the scenario of growing genetic inequalities pose a fundamental problem? Some analysts say that it does not. They argue that parents have always sought to provide advantages for their children and that IGM is just another prospective way to improve their children's life opportunities. Lee Silver, a biologist on the faculty of Princeton University, contends, for example, that anyone who accepts the right of affluent parents to provide their children with an expensive private school education cannot use "unfairness" as a legitimate basis for rejecting IGM. He acknowledges that individual uses of the technology, grounded in personal freedom and the right to reproductive choice, could have

dramatic, unintended long-term social consequences, but he is not unduly concerned.[36]

But IGM clearly is not equivalent to private schooling or piano lessons or any of the other benefits that affluent parents frequently provide for their children. Erik Parens, a philosopher at the Hastings Center who was a member of the AAAS working group, suggests thinking about the issue as the difference between purchasing new "tools" and purchasing new capacities. Thus while the privileged have always had access to "tools" like better schools, which conferred an advantage, the benefits of having these tools were limited by their native capacities, that is, their draw in the genetic lottery. In contrast, germ-line modifications, particularly for enhancement purposes, would enable the affluent to "rig" the genetic lottery and make some individuals doubly strong competitors for many of life's goods. He foresees that germ-line enhancements would likely widen the "already obscene gap between those who have and those who don't."[37]

What might be the ultimate consequence of growing inequalities through intergenerational genetic modifications? In *Remaking Eden,* Lee Silver offers a vision of a future dystopia in which germ-line engineering has significantly modified human characteristics and given rise to a castelike social structure with polarization between the unimproved "Naturals" and the "Gene-enriched" or "GenRich." He predicts, perhaps half-seriously, that eventually several species of human beings with fundamentally different capabilities and characteristics will develop, depending on whether and how groups have been enhanced.[38] Silver argues that advances in science and technology already under way combined with a commitment to individual freedom and a capitalist market economy, make his apocalyptic vision inevitable, if not in the near future at least in the centuries ahead.[39]

Maxwell Mehlman, a faculty member at the Case Western Reserve University School of Law, also anticipates that the outcome of current trends could be to create a two-tiered society. Mehlman's scenario foresees a society divided between those with access to genetic services and "a genetic underclass whose members, except when they escape through rare instances of intermarriage, remain enslaved to their genetic endowments." According to Mehlman, "As more and more advances in genetic therapy and enhancement techniques take place, the differences between the two groups will widen. Eventually, the degree of disparity will dwarf the social distinctions that characterized feudalism, the caste system in India, and even human slavery."[40] In a 1998 book entitled *Ac-*

*cess to the Genome: The Challenge to Equality,* Mehlman and his coauthor Jeffrey Botkin, a professor of pediatrics and medical ethics at the University of Utah, write about the development of a "genobility" based on selective access to genetic technologies. In their scenario, one group would be virtually free of inherited disorders, with access to genetic therapies for acquired diseases and the further benefit of being engineered for superior physical and mental abilities. The second group would be relegated to continue to suffer from genetic illnesses, receive less effective conventional medical treatments, and be confined to traditional approaches to self-improvement.

In contrast with Silver's trumpeting the inevitability of moving toward the dominance of a genetic elite in a brave new world, Mehlman and Botkin offer their alarmist vision as a means to propel ethicists and policy makers to deal with this challenge. Are there options that might at least blunt the impact of genetic technologies on equal opportunity? Are there ways to avoid allocating scarce genetic technologies on the basis of current social and economic advantages, short of banning the use of germ-line modifications? One approach Mehlman suggests is to make access to genetic technologies universally available. To reduce the cost, the government could, for example, regard these technologies as a public service and regulate their providers. Alternatively, if public funding is made available for the research, the government could seek to hold the patents for at least some of the innovations and license their distribution in order to hold down costs and promote widespread access.[41]

Mehlman and Botkin also consider a form of reverse discrimination that would give persons with fewer genetic endowments preferential access to genetic enhancements so as to promote upward social mobility. They recognize, however, that this approach might also appeal to eugenics advocates as a way to improve the human gene pool.[42] Moreover, given our social history, it seems more likely that those advocating human genetic engineering would prefer to invest scarce genetic resources to upgrade those considered to have superior genes still further.

A less problematical way to provide greater equity would be to declare access to at least some types of genetic services a "fundamental right" and fund it through universal health care. However, this option seems unlikely, particularly in the United States, which is the only economically advanced country that does not currently provide a universal entitlement to basic health care. Unless the cost of genetic services was substantially reduced, it would also be prohibitively expensive to offer free and equal access to a wide range of genetic therapies.

Mehlman and Botkin propose the use of a lottery system as the best way to level the genetic playing field. The lottery would be open to everyone on a voluntary and equal basis. Winners would receive access to a complete package of genetic services—all those available from the market—from which they could choose what they desired. The lottery and the services provided to winners would be financed by a special tax on manufacturers, distributors, and providers of genetic technologies.[43] But even this approach has problems beyond its obvious political unattractiveness. Presumably the lottery would function side by side with a free market in genetic services available to those with the requisite financial resources. Thus, at best the proposed lottery system would only compensate in a small way for the ability of the affluent to purchase genetic enhancements.

## Introduction of Genetic Enhancements

The analysis above distinguishes between the application of IGM for enhancement purposes, that is, nondisease-related interventions intended to improve what are already "normal" genes, and IGM to eliminate genetic mutations causing disease and disability. Some scientists and analysts anticipate that the ability to improve what are already "normal" genes may be available at some point in the future. The scenarios offered by Silver, Mehlman, and Botkin are predicated on the belief that IGM will include the ability to engineer enhancements that are socially advantageous and relatively low-risk. Others take issue with this assumption. There are very serious technical barriers to enhancement modifications. Amplifying or enhancing a normal trait would necessitate a far more sophisticated knowledge than we currently have about how genetic factors contribute to our physical and psychological traits. Because physical and behavioral traits are polygenic in nature, enhancement interventions would require the technical ability to modify several genes simultaneously or in very close sequence. Ethicist Thomas Murray, president of the Hastings Center, also points out that the complex traits that are most valued in human beings, like intelligence, creativity, sociability, and leadership, are not strictly or solely genetically determined.[44]

In recent years, some analysts have questioned the validity of making a sharp distinction between therapy and enhancement in genetic medicine interventions. One reason is that over time the boundary will likely shift, with the result that interventions that currently are classified as enhancements may be-

come categorized as therapeutic in the future.[45] Philosopher Anita Silvers argues that the distinction between treatment and enhancement presupposes a notion of, and inadvertently valorizes, a concept of normality that is culture-bound. She also worries that a commitment to medical services that seek to normalize the functionality of those who have disabilities will invite coercive and costly practices.[46] Others have pointed to the arbitrariness of this dichotomy. One example often cited is the case of two smaller than normal male children, the first with a documented growth-hormone deficiency and the other a short genotype. The treatment/enhancement distinction appears to require the treatment of the first child, but not the second, because his shortness is not the result of an illness. Yet, in a culture favoring tallness in males, the second child would suffer disadvantages.[47] The AAAS working group concluded nonetheless that, despite these difficult borderline cases, the distinction between therapeutic applications and enhancement uses of IGM is valid, and its major findings, concerns, and recommendations are predicated on this dichotomy.

For more than thirty years, various thinkers have anticipated genetic interventions intended to enhance human beings and identified profound ethical and theological issues related to this undertaking. Paul Ramsey, a Methodist moral theologian, warned as early as 1970 in his book *Fabricated Man* that "playing God" with genetic technologies, particularly efforts to undertake genetic manipulation for eugenic purposes, would more likely result in human self-destruction than improvements in the species.[48] Other critics have had a less apocalyptic vision, but nonetheless share his deep reservations about human genetic enhancements. Many in the secular and religious communities therefore distinguish between the acceptability of somatic cell therapy, and possibly germ-line interventions as well, for therapeutic purposes and their inappropriateness for enhancement purposes.[49]

The analysis in this chapter underscores the profound implications that enhancement applications would have for increasing societal inequality and injustice. Therefore, it is relevant to question whether beginning IGM to correct for disease-related mutations would increase the likelihood of crossing the boundary between therapy and enhancement applications. Some analysts argue that any type of germ-line modification, even those intended to eliminate abnormalities, would send us down a slippery slope that inevitably would lead to genetic enhancements. This position, taken by Nelson Wivel and LeRoy Walters in a 1993 article, is predicated on the difficulty of maintaining a sharp dis-

tinction between therapeutic and enhancement applications of genetic alterations.[50] The fact that the technology for therapy and the technology for enhancement procedures are basically the same is yet another factor likely to promote creeping enhancement applications. Also, given the size of the potential market for enhancement applications, biotechnology and pharmaceutical corporations are likely to invest heavily in enhancement research and promote these applications. (On this point, see Chapter 19 in this volume on the effects of commercial considerations on IGM.) Thus it seems likely that going forward with IGM to treat disease or disability will make it difficult to avoid use of such interventions for enhancement purposes.

In theory, genetic enhancement could be accomplished through either somatic or germ-line intervention, but the desire to undertake enhancements will most likely favor germ-line over somatic technology. Genetic enhancements are likely to require altering several genes that work in concert with each other. For this reason the genetic intervention is likely to be more effective when conducted early in the development of the embryo or on the fetus in utero. In many, perhaps most, instances, such an early intervention would result in germ-line alteration whether or not it was intended.[51] Also, the very considerable expense involved might incline parents to try to get the most for their investment, again favoring the IGM option.

## Justice and the Provision of Genetic Services

A dilemma under an egalitarian or needs-based justice approach to health is defining the scope and nature of the societal obligation, that is, the type of services that should be provided to all members of society and the basis of this determination. More specifically, if and when IGM becomes available, does a just distribution of societal resources require that these procedures be included in the package of health care coverage provided through publicly funded health benefits or private health insurance? This issue is complicated by the difficulties of determining how extensive a package of benefits should be provided in view of the growing cost of all forms of medical services, particularly high-technology interventions. Currently, even affluent industrialized countries are experiencing problems in funding expensive health services through national health insurance institutions. It is also not possible at this time to anticipate the future costs of potential therapeutic or enhancement genetic applications or their potential contributions to good health and long life, but the history of

high-technology medical interventions suggests that IGM will be quite expensive.

A few philosophers have begun thinking about this knotty issue. Proceeding from a conception of justice based on a societal obligation to preserve fair equality of opportunity, Norman Daniels's position is that justice requires providing access to medical services that counter the natural disadvantages introduced by disease. In Daniels's influential theory of health justice, first put forward some twenty years ago, health care has "normal functioning" as its goal. Recognizing that genetic abnormalities can produce some of the most devastating and painful handicaps and disabilities, Daniels argues that just health care includes access to genetic services. His view, however, is that only services that restore departures from species-typical normal functioning meet a strict conception of medical need. He therefore proposes limiting interventions to treating serious impairments of physical or cognitive functioning. Enhancement, according to Daniels, does not meet a real medical need even when the service may correct for a competitive disadvantage that does not result from prior choices. He also cautions against the "futile goal of eliminating or 'leveling' all natural differences between people."[52] For him, medicine "has the role of making people *normal* competitors, not *equal* competitors."[53]

Daniels and a series of collaborators—Allen Buchanan, Dan Brock, and Daniel Wikler—reconsider the issue of the requirements of distributive justice in an age of genetic intervention in *From Chance to Choice: Genetics and Justice.* Like Daniels's earlier work, *From Chance to Choice* argues that genetic intervention to prevent or ameliorate serious limitations on opportunities due to disease is a requirement of justice. Also like Daniels's earlier writings, the book advocates societal efforts to eliminate genetically based deprivations on equality of opportunity. Furthermore, the book maintains that justice may require regulating the conditions of access to genetic enhancement to prevent exacerbation of existing unjust inequalities. Going beyond Daniels's earlier views, the authors conclude that, at some point in the future, conceptions of equality of opportunity may require interventions that are not necessarily limited to the cure or prevention of disease. They point out that successful and widespread efforts to undertake genetic enhancement could result in changes in perspective about the range of normal human functions, altering distinctions between health and disease and between enhancement and treatment.[54] Given this potential for ratcheting up the standard for normal species functioning, they believe that it is not inconceivable that we would come to reclassify any cor-

rectable genetic condition that has a significant adverse impact on equality as a form of disease.[55]

In an article written in the early 1990s, the philosopher Leonard Fleck also argues that powerful considerations of justice require the development and dissemination of many, but not all, of the emerging genetic technologies.[56] Like Daniels, Fleck distinguishes between technologies that have the goal of treating disease and disability and those intended for the enhancement or improvement of human traits. He sets up a hypothetical situation based on the existence of a national health insurance system like Canada's and the development of effective IGM without the corresponding development of somatic gene therapy (which is a very unlikely scenario). Within this context, he concludes that germ-line genetic engineering aimed at eliminating deleterious genes and replacing them with their properly functioning version would have a strong claim on societal health resources. According to Fleck, eliminating deleterious genes would have a greater ability than any other medical intervention to restore fair access to a normal opportunity range for individuals who would otherwise suffer profound disabilities or premature death. Fleck also assumes that no remedial social policy or more just social practices can effectively correct for these disadvantages,[57] which is a point of view with which many in the disability community would likely disagree. He therefore characterizes the moral claim to germ-line therapy as much stronger than access to virtually all the very expensive halfway life-prolonging technologies that are the hallmark of contemporary medicine.[58] Assuming that a choice would have to be made between funding a very large potential demand for somatic and germ-line gene therapy, he opts for the latter on the grounds that shifting resources to the future generations would be a more effective form of social investment.[59] In return, he suggests that future generations would reciprocate by making fewer claims on health resources,[60] but this may be of little comfort to those who would have to sacrifice their own claims in order to facilitate an intergenerational transfer of resources.

In more recent writing, Fleck deals with a related issue, whether future possible children have a just claim to a sufficiently healthy genome.[61] He focuses on the issue of allocating fair access to preimplantation genetic diagnosis to avoid the birth of children who carry a gene for a serious medical disorder. The cost of achieving a successful pregnancy via preimplantation genetic diagnosis is currently about $40,000, considerably less than IGM is likely to be, but still beyond the means of the majority of persons. Given the potential costs of mak-

ing this therapy widely available, Fleck recommends restricting socially funded access to preimplantation diagnosis to couples who know they are at risk of having a child with a serious genetic disorder, which could potentially adversely affect both the length and quality of life of a prospective child. He lists cystic fibrosis, Duchenne muscular dystrophy, Carnavan disease, fragile X syndrome, hemophilia, juvenile diabetes, Tay-Sachs, autism, neurofibromatosis, and Lesch-Nyhan syndrome as appropriate diseases for which to screen. Even with these limitations, he estimates the initial cost is likely to be upwards of $8 billion a year, which would then be offset by the societal savings achieved through not having to provide expensive medical and social interventions for the children who otherwise would be born with these problems. Wider societal screening to avoid all births of children with a gene for a serious disorder could cost an additional $160 billion a year, a staggering figure that Fleck quite rightly believes cannot be justified on either moral or economic grounds.

So does a just distribution of societal resources require that IGM, if and when it becomes available, be part of a package of universally available health care benefits provided by either the state or private insurers? A final determination would depend on a number of factors, including efficacy, cost, and the alternatives available, but it is difficult to envision a scenario in which a commitment to justice would require funding these interventions. I believe that there is a far stronger rationale for providing access to preimplantation diagnosis or perhaps to somatic gene therapies if and when they become effective than there is to subsidizing germ-line intervention. Currently, most candidates for somatic genetic treatments do not have alternative therapies available. This is not true of IGM.

What about subsidizing IGM for enhancement purposes, as Buchanan, Brock, Daniels, and Wikler propose? I don't agree with their analysis or the conclusions they draw. A scenario in which IGM were to be a viable intervention, but available only to those with the financial means to afford it, would undoubtedly aggravate social inequality within developed nations. Yet, as the discussion on access pointed out, making enhancement interventions universally available in theory would not make them equally accessible in fact. Even in the very unlikely situation that wealthy countries could afford to subsidize universal access, those who are educated, resident in areas with sophisticated medical centers, and otherwise advantaged would be more likely to be able to capitalize on these opportunities. Moreover, since genetic interventions for enhancement purposes would be problematic, it is a bad idea to stimulate use of them.

Such policies would also significantly increase disparities between industrialized, affluent countries and the rest of the world. Fortunately, it seems quite unlikely that there will be successful and widespread development of enhancement technologies as they assume. The preferable and more equitable way to proceed would be to restrict all applications of enhancement technologies rather than to seek to make these technologies more widely available.

## International Dimensions

Most analyses of the justice dimensions of health care focus on a national context, perhaps capable of being generalized to countries at a similar level of development, but in a world in which globalization is increasing, it is also important to assess the international implications of new technologies. Here it is relevant to note that the 1978 Alma-Ata Declaration, made by participants at an international conference on primary health care sponsored by the World Health Organization, noted that then existing gross inequality in the health status of people, particularly between developed and developing countries, as well as within countries, is politically, socially, and economically unacceptable, and is therefore of common concern to all countries.[62] Unfortunately and tragically, the passage of time has accelerated these inequalities. Economic globalization, with its tendency to aggravate economic disparities, and the disparate impact of the HIV/AIDS pandemic on poor countries has made matters far worse.

A recent interpretation of the human right to health in the form of a general comment (a legal interpretation) adopted by the United Nations Committee on Economic, Social and Cultural Rights draws attention to the international obligations of states to take steps, individually and through international assistance and cooperation, toward promoting the realization of the right to health in other countries. The general comment directs countries legally bound by the jurisdiction of this committee (which currently includes most advanced economies, with the exception of the United States, which has failed to ratify the International Covenant on Economic, Social and Cultural Rights) to facilitate access to essential health facilities, goods, and services in other countries, whenever possible, and to provide the necessary aid when required. It also notes the importance of taking measures to prevent violations of this right in other countries.[63]

As someone who was involved with the drafting of this instrument, I am aware that the members of the UN committee were not thinking about genetic

technologies when they wrote these paragraphs. Nevertheless, I believe the obligation to prevent violations of the right in other countries, even by third parties, may have some application to the subject of this chapter. Going forward with IGM would likely further increase the disparities between developed and developing nations, just as it would disadvantage the poor and those with moderate incomes within specific countries. It could consign poorer countries to a lesser standard of health, with fewer prospects of catching up with other societies.

Less-developed countries lack both the resources and the infrastructure to conduct complex genetic interventions. Most cannot offer even the most basic health services to their populations, particularly those living in rural areas. Efforts to respond to the HIV/AIDS pandemic have seriously strained their limited health care infrastructure. Thus, even if more scientifically advanced countries were to be willing and able to make the technologies for IGM available without cost—and this seems very unlikely in an age of strict intellectual property protection—poor countries in Asia, Africa, and Latin America, and likely a majority of middle-income countries as well, would not be able to take advantage of the offer. Nor should they, given the likely cost and the problems it would introduce. A few centers may open in some of these countries offering IGM. Very likely they would cater to the rich or super rich and operate without any regulatory supervision. And those with the means might seek access to enhancement technologies in other countries.

Even if this scenario does not amount to a clear violation of the right to health, it would result in a world with considerably greater injustice. The overwhelming majority of less-developed countries have been economically disadvantaged by economic globalization. IGM offers the prospect that they would be disadvantaged in the genetic and health sphere as well, particularly if enhancement technologies were to be available to a significant cross section of the population in affluent industrialized societies. One consequence would be to make the citizens of poor countries even less able to compete.

## Conclusion

The majority of the members of the AAAS working group on human inheritable genetic modifications recommended that the introduction of such interventions be contingent on resolving ethical and justice issues. This chapter highlights how difficult it is to do so.

The introduction of IGM in any form would have serious adverse implications for an egalitarian or needs-based approach to justice. IGM would be particularly problematic if it were to be introduced into a health care system that does not provide universal access to key health care services or regulate closely the packages offered and the practices of private health insurers. Fundamental health care reform does not seem a likely option in the foreseeable future in our country, and, even if it were to take place, IGM would still increase inequality and discrimination. Moreover, even countries recognizing a right to essential or core health care services, like the western European democracies and Japan, would unlikely be able to afford providing IGM to a broad cross section of their population. IGM would also magnify the genetic gap between the affluent countries that would be able to afford IGM and the majority of poor nations unable to do so.

The opening to this chapter posed the question of whether the likely impact of IGM constituted a sufficient challenge to considerations of justice to warrant recommending against proceeding with such interventions. I think that it does. The analysis in this chapter underscores that even if IGM can overcome the scientific hurdles outlined in this volume, it would have profound negative societal consequences. IGM would very likely make current injustices and inequalities worse and far more difficult to rectify. Nor does it seem feasible to rectify these problems through other policy measures. From a justice perspective, there seems to be only one option: not to go forward with the development and application of IGM.

ACKNOWLEDGMENTS

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NOTES

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2. This point is made in Allen Buchanan, Dan W. Brock, Norman Daniels, and Daniel Wikler, *From Chance to Choice: Genetics and Justice* (Cambridge: Cambridge University Press, 2000), 20–22.

3. Tom L. Beauchamp and James F. Childress, *Principles of Biomedical Ethics,* 4th ed. (New York: Oxford University Press, 1994), 327.

4. Ibid., 328.

5. David Resnik, Holly Steinkraus, and Pamela Langer, *Human Germline Gene Therapy: Scientific, Moral, and Political Issues* (Austin, Tex.: R. G. Landes, 1999), 130–31. Their listing is based on Robert Nozick, *Anarchy, State and Utopia* (New York: Basic Books, 1974).

6. Ibid., 330.

7. An example of this perspective is Lee M. Silver, *Remaking Eden: How Genetic Engineering and Cloning Will Transform the American Family* (New York: Avon Books, 1998).

8. An earlier AAAS project defining a human rights approach to health care reform proposed such a definition of a right. See Audrey R. Chapman, *Exploring a Human Rights Approach to Health Care Reform* (Washington, D.C.: American Association for the Advancement of Science, 1993).

9. Article 25 of the Universal Declaration of Human Rights states that "everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including food, clothing, housing and medical care and necessary social services." The further development in Article 12 of the International Covenant on Economic, Social and Cultural Rights is the recognition of "the right of everyone to the enjoyment of the highest attainable standard of physical and mental health." The General Comment of the UN Committee on Economic, Social and Cultural Rights which interprets this right specifies obligation of states to provide at the least basic health services, preventive health measures, environmental protections, and measures to control and treat epidemic and endemic diseases.

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20. Robert Pear, "After Decline, the Number of Uninsured Rose in 2001," *New York Times,* September 30, 2002, A-21.

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27. Maxwell H. Mehlman, "Access to the Genome and Federal Entitlement Programs," in *The Human Genome Project and the Future of Health Care,* ed. Murray, Rothstein, and Murray Jr., 113–22.

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37. Erik Parens, "Justice and the Germline," in *Engineering the Human Germline,* ed. Stock and Campbell, 122.

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58. Ibid., 150.

59. Ibid., 142–47.

60. Ibid., 148.

61. Leonard M. Fleck, "Just Caring: Do Future Possible Children Have a Just Claim to a Sufficiently Healthy Genome," in *Medical and Social Justice: Essays on the Distribution of Health Care,* ed. Rosamond Rhodes, Margaret Battlin, and Anita Silvers, forthcoming.

62. Article II, Alma-Ata Declaration, Report of the International Conference on Primary Health Care, Alma-Ata, September 6–12, 1978; the text is reproduced in the World Health Organization, Health for All series, no. 1 (Geneva: WHO, 1978).

63. Committee on Economic, Social and Cultural Rights, "General Comment No. 14. The right to the highest attainable standard of health," adopted in 2000,UN Doc. E/C.12/2000/4, paras. 38–39.

CHAPTER TEN

# The Hidden Eugenic Potential of Germ-Line Interventions

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## The Universality of Trained Incapacity

In the early part of the twentieth century, Thorstein Veblen coined the term *trained incapacity,* which unfortunately has fallen from use. The misfortune is substantial, because while the term is rarely deployed, the social phenomenon that Veblen was characterizing is more a feature of the professions and disciplines today than in his times.

Professions, Veblen pointed out, train their members or practitioners to see certain aspects of a problem, but in so doing those practitioners become trained to *not see* other aspects of a problem. Thus by the nature of the training, we are typically blind to the subtle and sometimes subterranean workings of a disciplinary or professional perspective and its implications—unless or until someone outside the "tunnel" calls it to our attention. Nowhere is this more poignantly and sometimes fatally clear than in medical diagnoses. The medical specialist who focuses on one internal organ (e.g., liver ailments) can become so narrow that he or she is bound by a bias in perspective to miss a critical diagnosis of the malfunctioning of another part of the body. Medical mis-

takes account for more than 100,000 deaths annually in the United States alone, and the *New England Journal of Medicine* recently published a study estimating that more than 11,000 heart attacks are misdiagnosed.[1]

Trained incapacity is no less a feature of professional and disciplinary perspectives on social, economic, and political problems. Veblen was trained as an economist, and he was profoundly aware that his profession's concentration on market forces often blinded it to other explanations of behavior in the market. No one escapes trained incapacity in this formulation, precisely because all professionals are guided by a perspective that strongly inclines them to hone in on some matters—and by that very process, forces them to exclude, ignore, or simply not even consider other factors.[2] For psychologists trained to focus on the psyche of the individual, that gaze can often make them oblivious to larger structural forces in the social context that might shed as much light on the individual behavior or individual condition. For example, during the Great Depression, many men were diagnosed as *clinically* depressed but only in hindsight was the connection to economic depression so obvious. Sociologists, on the other hand, concentrate so much on organizational and institutional structures and group relations that they often develop the trained incapacity to recognize a potentially serious individual problem that a psychiatrist or clinical psychologist is far more likely to recognize.

Thus, when I turn now to what I will characterize as the trained incapacity of bioethicists, I do so not to exceptionalize or draw a caricature of this enterprise, but to show how the domination of a perspective from a field of inquiry can produce systematic and unwitting blind spots that generate their own sets of unexamined ethical and social problems.

## The Trained Incapacity of a Bioethicist's Perspective

There is an overwhelming tendency for ethicists, medical specialists, clinical geneticists, philosophers, and the best-intentioned guardians of a notion of rights and obligations in Western societies to concentrate their ethical gaze on the states of minds and physical conditions of individuals—to the near exclusion of the fate of social groupings to which individuals belong.

In an influential treatise on reproductive choice, for example, John Robertson[3] acknowledged that social and economic constraints such as access to employment, housing, and child care might play a role in the decision to have a child. However, the overarching theme, to which he returns again and again, is

that reproduction "is first and foremost an individual interest."[4] This is not to suggest that all bioethicists concentrate primarily or exclusively on individual issues of autonomy and decision making. Rather, those bioethicists who do engage the group level (of effects, concerns, and group autonomy) do so at the margins.

There are certainly good reasons for this kind of professional bias that can appropriately rivet our attention to the individual. For example, from one perspective, medical experimentation does occur on individuals. Some of the earliest informed consent requirements for the protection of human subjects originated out of a concern that *individuals* be informed about any experiments performed on them, and indeed, that individual participation in such experimental medical and scientific research be contingent on individual consent given freely and willingly.

Yet through another lens, medical experimentation also tends to occur on certain groups of individuals more than other groups of individuals. The history of the birth control pill, being tried out first on Puerto Rican women before it was used in the continental United States, is but one of many such examples. The infamous Tuskegee study, which was the major trigger event for requirements for informed consent for human subjects in the United States, was performed mainly on a cluster of individuals, all of whom, through this lens, just happened to be African Americans.[5] Less well known is the fact that for decades the recommended dosages of x-rays administered to African Americans were usually one and a half times, often double, those administered to whites. While these x-rays were administered to individual blacks, the recommended dosage level was to all those classified into that group. An ethic of health care that required x-ray technicians to first obtain the informed consent from individual African Americans would entirely miss the point about the consequences variably affecting the fate of this group, *as members of a group.* These higher doses of radiation might well affect the germ line—much as we now have evidence that diethylstilbestrol (DES), a synthetic estrogen, probably affects the germ line. From 1946 to 1971, pregnant women in the United States frequently took DES on the recommendations of their family physicians—sometimes to reduce morning sickness.[6] The practice was discontinued in 1971, when research revealed substantially high rates of a reproductive tract tumor, vaginal adrenocarcinoma, in the daughters of women who had taken DES. But there is a striking difference. DES was administered to pregnant women of all social groups, ethnicities, races, and cultures (in the United States).[7] The vari-

able effect on the germ line was (relative to the x-ray administration) random. But the effects of systematically higher doses of x-rays on African Americans may actually concentrate germ-line effects in that group.

The knotty problem that bioethicists have regarding the group is the social and political conundrum created in trying to determine who speaks for the group in matters of informed consent. At least for individuals, we have a clear focal point for discussion.[8] Groups are composed of individuals with a range of views from disagreement to consensus. This is the case within religious groups, ethnic and racial groups, and disease groups and affects those politically mobilized on behalf of any of these groups.

The way in which the institutional apparatus of the society is mobilized (or harnessed) will determine whether the individual is the most important unit of analysis in explaining or assessing a course of action. For example, if one happens to be an individual with a relatively rare genetic disease, the amount of funding targeted for research to diagnose, treat, and cure that disease is likely to be much lower than if one's disease is more common.[9] This is true whether the public or private sector is financing the research and treatment. Since profit is driving private-sector initiatives in this arena, there is little motive to develop treatments for rare disorders. For the public sector, one can make the strong argument for allocating tax dollars in an efficient manner, to produce the greatest good for the greatest number. But these are only the most obvious of ways in which the individual is not the right level or unit of analysis for explaining the behavior of researchers, or of clinical geneticists, or of bioethicists.[10]

Since social groups are stratified, access of certain groups to political power is also an important determinant of whose disease gets funded for research. Funding patterns for research and treatment of genetic diseases reflect this interplay between group interests and group power and health care priorities. In 1967, muscular dystrophy and cystic fibrosis were funded at much higher levels than sickle cell anemia research.[11] However, from 1968 to 1972, political mobilization by African Americans (and later in behalf of African Americans) produced a dramatic increase in funding levels for research and treatment for sickle cell anemia. In direct reaction to this, the Italian American community was mobilized shortly thereafter to seek and obtain increased funding levels for their genetic disease—Cooley anemia (also named beta-thalassemia).

In 1972, the National Sickle Cell Anemia Control Act was signed into law, with an authorization of over $100 million for the establishment of screening and counseling programs and for research. While state laws mandated screen-

ing and sometimes provided limited funding for these programs, support at the federal level engendered interethnic group competition, envy, rivalry, and increasing demands for "our fair share" of concern and money.[12] People from the Mediterranean, especially southern Italy, are at greater risk for beta-thalassemia (Cooley anemia). As it became clear that blacks were going to get research and treatment for their disease funded, the Mediterranean constituents of Congressman Giaimo persuaded him to introduce a bill, also in 1972, for a National Cooley's Anemia Control Act. That bill passed. Ashkenazi Jews are at greater risk for Tay-Sachs than any other group, and within a few months, a Jewish constituency put pressure on Senator Javits to secure passage of a National Tay-Sachs Control Act.

At this point, a very interesting controversy surfaced. Should there be a proliferation of laws and programs tailored to specific inherited disorders, or should there be a centralized program, with one omnibus law? Initially, Javits and others moved to introduce and support a separate bill for Tay-Sachs. Later, they became persuaded that a single comprehensive bill covering all disorders should be developed. From a review of testimony at congressional hearings on the bills, it is clear that blacks almost uniformly testified in favor of keeping the national legislation for sickle cell separate (U.S. Senate, 94th Congress, 1975). They argued that a composite bill would dilute the interest, concern, and funding for sickle cell. They feared that control of the sickle cell program would shift farther and farther away from African Americans. But the medical establishment brought out all of its artillery to these hearings and argued the language of *efficiency* quite effectively. They won, and Congress passed the National Sickle Cell Anemia, Cooley's Anemia, Tay-Sachs, and Genetic Disease Act in 1976, the conglomerate result of this ethnic/racial lobbying for disease-specific funding. (See Table 10.1.)

This is an example of the role of group interests and group power in the development of knowledge about genetic conditions. It is a development that can stymie and befuddle bioethicists when it comes to generating a set of ethical principles for molecular or population genetics researchers who want to "do genetics" on human population groups such as Native Americans in the United States, Aborigines in Australia, and First Nations People in Canada. As they learned, obtaining informed consent from these and other groups—to participate in the Human Genetic Diversity Project—was a politically challenging task. Modern postindustrial societies are exceptional in the way in which authority to make the decision to participate (or to refuse to participate) in ge-

*Table 10.1. NIH Research Fund Spending, by Disease*

| | Number of People Afflicted in the United States | Total Research Funds (in U.S. dollars) | Spending per Patient (in U.S. dollars) |
|---|---|---|---|
| Diabetes | 16,000,000 | 313,334,000 | 19.58 |
| Coronary heart disease | 13,670,000 | 285,150,000 | 20.86 |
| Alzheimer disease | 4,000,000 | 314,159,000 | 78.54 |
| Kidney disease | 3,512,000 | 203,677,000 | 57.99 |
| Breast cancer | 1,953,000 | 409,545,000 | 209.71 |
| Parkinson disease | 1,000,000 | 34,218,000 | 34.22 |
| Prostate cancer | 968,000 | 94,614,000 | 97.70 |
| Scleroderma | 500,000 | 3,570,000 | 7.14 |
| AIDS or AIDS virus | 775,000 | 1,862,529,000 | 2,403.26 |
| Cystic fibrosis | 30,000 | 62,056,000 | 1,068.53 |
| Sickle cell anemia | 82,500 | 48,600,000 | 590.00 |

*Source:* National Institutes of Health, Centers for Disease Control and Prevention
*Note:* NIH estimates for fiscal year 1997.

netic research resides in the individual. Many societies give that authority to larger units—to the head of the family, the tribe, the village, and so on. So when Western-trained researchers (with the approval of their local bioethics review committee) descend on a village to gain the cooperation for such work, the major ethical question—to whom should they turn for consent?—surfaces in new ways.

Since ethical principles for conducting human molecular genetic research have been developed and approved in the West, with an insistent focus on individual autonomy and consent, we have produced a trained incapacity to engage this issue successfully at the group level. Rather, the temptation is great to simply enumerate the problems generated by opening the Pandora's box of consent that is not given at the individual level, express despair at the putative quagmire of ethically discerning who speaks for whom in the group, and move back to the individual as the only workable site for resolution.

## Genetic Diseases and the Fracture of the Public Health Consensus

Before 1962 and the emergence of testing and screening for genetic diseases in the U.S. population, there was a widely accepted public health consensus on

what constitutes the public good and the public interest in eradicating such health problems as smallpox, tuberculosis, yellow fever, and cholera. Increased sanitation enforced by the state or quarantine (as needed, with smallpox) was an achievable public policy development. However, with the documentation of the extent to which genetic disorders cluster in risk populations that coincide with ethnic and racial groupings, the public health consensus would be sharply and critically undermined. Now, as we have seen, groups would come forward to press for more research on "their" disease.

The past decade has witnessed the creation of genetic tests with high rates of sensitivity to some ethnic and racial groups, but low sensitivity to others. Zuni Indians have an incidence rate of cystic fibrosis similar to that of Americans of North European descent. Yet there is no genetic test available for the particular form of cystic fibrosis most likely to afflict the Zuni. In spite of this, and in spite of the high variability in the sensitivity of the test to different population groups, as reflected in Table 10.2, the National Institutes of Health Cystic Fibrosis Consensus conference (held April 14–16, 1997) recommended that all couples expecting children be given access to the test for the DF508 mutation. The significance of this recommendation for a discussion of the hidden social implications for germ-line interventions will be addressed later in this chapter. I now want to turn to and further explore background issues for locating the appropriate unit of analysis in discussions of autonomy and choice.

While it is true that individuals make choices, they do so in a social and economic context that can be powerfully and demonstrably coercive.[13] While relatively obvious when we look at other societies, it is less understood when we look at our own society—albeit substantially obscured because this individual choice is deeply embedded in the taken-for-granted assumptions about what

*Table 10.2. Variation in Sensitivity to Genetic Testing for Cystic Fibrosis*

| Group | Incidence | Carrier Frequency | % DF508 | Sensitivity |
|---|---|---|---|---|
| Caucasians | 1:3,300 | 1:29 | 70 | 90 |
| Ashkenazi Jews | | 1:29 | 30 | 97 |
| Zuni | 1:1,580 | | | |
| Hispanics | 1:8,500 | 1:46 | 46 | 57 |
| African Americans | 1:15,300 | 1:63 | 48 | 75 |
| Asian Americans | 1:32,100 | 1:90 | 30 | 30 |

*Source:* National Institutes of Health Consensus Conference on Genetic Testing for Cystic Fibrosis, April 14–16, 1997, Washington, D.C.

is "normal" in one's own culture. For example, long before the advent of prenatal detection technologies, preference for a male child in India was so great that a notable fraction of the population practiced infanticide of newborn females. Once technologies for prenatal determination of sex became available, the quest for disclosure took an even more ominous turn.

In 1971, India passed the Medical Termination of Pregnancy Act, which stipulates that a woman can be given an abortion only if there is a life-threatening situation or a grave injury to her physical or mental health.[14] Amniocentesis began in India in 1974, but there were early reports that the test was being used less to detect birth defects than to determine the sex of the fetus. The Indian Council of Medical Research requested that this practice be discontinued. While the New Delhi clinic complied with the request for the most part, private clinics sprung up in several cities to fill the very determined requests for prenatal knowledge of a fetus's sex. Within two years, more than a dozen such places were in operation all over India.

In August 1994, the Indian Parliament passed a new law that stiffened the penalties for screening the fetus to determine the sex. The law imposes a three-year prison sentence and a fine of approximately $320 for administering a test with the sole purpose of prenatal sex determination. However, there was a loophole so large that the law is practically unenforceable—and the practice continues at such a high rate that in Haryana, a populous northern state, the sex ratio is an astonishingly low 874 females to every 1,000 males.[15]

It should be clear from the above examples of sex selection preferences in India that what appear to be individual familial choices may often be better understood as empirical social patterns reflective of the social and cultural hegemony. For example, in early 1994, *Nature* published "China's Misconception of Eugenics,"[16] an article that portrayed the Chinese government's policy of trying to prohibit couples with certain diseases from procreating as having a distinctively distasteful eugenic quality. While the article was forthright in denouncing the use of state power as the vehicle for discouraging procreation, it implied that a personalistic and individualistic decision to interrupt a pregnancy is "voluntary" by observing that "China's plans for eugenics must be judged by the degree to which they interfere with people's wishes; they may not differ much from programmes followed elsewhere but compulsion will make them unacceptable."[17]

Yet, before we leap to the conclusion that this is a simple binary matter of voluntarism versus state power, there is considerable evidence to support the

observation that what we characterize as personalistic and individualistic decisions in Western societies are on closer inspection (just as with sex selection in India) actually very remarkably socially patterned. Thus, the situation is not reducible to an either/or formulation. A continuum is a better analytic device for depicting an array of strategies and options, from individual choice to embedded but powerful social pressures (stigma and ridicule)—and from economic pressures (fear of loss of health insurance, or even of inability to obtain such insurance) to the coercive power of the state to penalize.

## Locating the Appropriate Unit of Analysis: Individual versus Social

We have already noted examples of how this refusal to address the matter of informed consent at any other level than that of the autonomous individual gets bioethicists into twists and contortions when they must deal with non-Western cultures. But there are also subtle and unexamined ethical issues inside Western societies when we insist on ignoring the social reality of group interests and, possibly, the need for some element of group consent. I am not suggesting that obtaining such consent will be easy, or even that the conceptualization of group boundaries and group interests will be universally possible. That is also true for the individual, when it comes to minors, indigent persons, mentally incapable persons, and so on, *but we find ways* for the purposes of further action.

This professional refusal to address group interests can come home to haunt bioethicists' reflections, decision making, and recommendations. For example, a review panel with the responsibility for the protection of human subjects is often given a protocol for research, in which the only relevant unit of concern is the individual. This can be a misplaced focus of ethical concern. Here is a case in point.

Huntington's disease is a late-onset neurological disorder that strikes usually after the age of 35–40. The race to locate the Huntington gene(s) resulted in a triumphant discovery in the early 1990s.[18] There is now a genetic test that can be performed to determine whether the person at risk for the disease actually carries the gene. Within a few short years of the discovery, neuroscientists in Denmark published a study in which they concluded that males with Huntington's disease are twice as likely to commit crimes as those who do not have the disease.[19] The authors report that when they applied for permission to pur-

sue this research they made it clear to the human subjects review panel that no individuals would be harmed by participating in the study. They also noted that when analyzing the data, only serial numbers were used and all personal identifiable information was removed.[20]

Yet this research report can implicate all those males in a group category (i.e., all those diagnosed as having Huntington's disease). This number will include far more people than those individuals who "participated" in the statistical manipulations that were the fundamental methodological techniques used in the study. The deeply embedded assumption of the ethics committee is that if no harm is done to the individuals participating in the study, then there are no other ethical questions that deserve scrutiny or consideration. Nevertheless, the results of the study implicate and potentially stigmatize all those with Huntington's disease. To the extent that the researchers find evidence that there is a general association between crime and Huntington's disease, then all those persons in that group who have Huntington's disease are vulnerable to being stigmatized by this association. I am not suggesting that this study actually established a strong link between criminal activity and Huntington's disease; that is a topic for a different analysis. Rather, what is most important for this line of argument is that the human subjects protection committee does not even have on its agenda a radar screen for picking up the matter of group interests (all those males with Huntington's disease) in its review of the research protocol. Understandably, the institutional review board would have a difficult time determining and establishing who speaks for the group (all those males with Huntington's disease) in such a situation.

## Background to the Individual/Group Focus with Single Nucleotide Polymorphisms

A map of the genome allows researchers to locate a piece of DNA, but that map will not indicate the precise arrangement of the nucleotides in that DNA. This arrangement, or linear order, of nucleotides is called the DNA sequence. The DNA sequence is important because different sequences encode different information. One of the main reasons for studying DNA is because it encodes information that specifies how cells should make biologically useful molecules, such as proteins.

If we compare the complete DNA sequence of any two people, we will find a difference approximately one time in every thousand nucleotides. The sim-

plest kind of difference is when one nucleotide differs between the two people—for instance, when one person has a G at a certain position in the sequence and another person has a T there. In some cases, such differences will cause a slightly different protein to be made. In other cases, these differences have no known impact on which protein is made or on any other biological functions.

Places where people's genomes differ by one nucleotide are called single nucleotide polymorphisms, or commonly SNPs. The search for SNPs is now in full bloom because they can be used as markers on chromosomes. These markers can be used to make genetic maps that may allow us to locate genes of interest, such as those involved in diseases. But they can also be used to identify and mark both individuals and groups of individuals, a technological capacity that will prove to be of extraordinary significance and consequence to social studies of science.

## SNPs on Chips

Many things that molecular geneticists want to study, including many (if not most) human diseases, are caused by a complex interaction between environmental factors and an individual's biology, including different genes. In the past decade, media accounts of the gene for this or that disease, condition, attribute, or behavior have become common, sometimes being reported weekly. This has led many lay persons to believe that a single gene is the cause of a host of diseases, attributes, and conditions.[21] Yet only in rare cases does a single gene have a very strong, identifiable effect on whether or not a person contracts or develops a disease. Such cases are generally called single-gene disorders.

In most cases, when genes play a role in the development of a disease, such as a particular kind of heart disease, the role of any single gene will be very small. To study the genetics of complex conditions such as heart disease, methods must be devised for finding a constellation of genetic differences between people who present with that disease. One method for examining many different pieces of DNA simultaneously and for detecting more than one genetic difference in a single experiment, is to put many different genes or parts of genes on a computer chip.

DNA chips are useful for doing the equivalent of 100 or even 1,000 experiments all at one time in one simple procedure. The chip with dimensions less than one square centimeter may have 1,000 or 10,000 different sectors. The

technology required to attach DNA of a slightly different sequence to each sector is now available. For instance, suppose that a group of researchers had found 2,000 different SNPs; that is, 2,000 identifiable places in the genome where people's DNA sequences could differ by one nucleotide. Then, somebody could make a DNA chip that would have all of the possible SNPs (at least 4,000, but it could be more because each SNP will have between 2 and 4 possibilities), each in its own separate and identifiable place on the chip. Then, if my DNA were exposed to the chip (actually, DNA or RNA is hybridized to the chips), one experiment could determine which SNP I had at all 2,000 different places in the genome. We could make a SNP profile for me. If we did this for 5,000 people, 2,500 of whom had a certain kind of heart disease and 2,500 of whom did not, then we might be able to find 5 to 10 SNPs that were correlated with a high likelihood of developing heart disease. That is the core of the methodological strategy of SNPs on chips.

## SNPs, Human Diversity, and Social Groupings

Approximately 85 percent of human genetic diversity can be found in any population, even a very small, village-size population.[22] For instance, if we were looking at SNPs, we would find that most are in all populations throughout the world. However, there will be some SNPs that are found in certain people from Finland but probably not in people of Native American descent. This does not mean that a certain sequence is found in all people from Finland, or that it is never found in people who are not from Finland.

The creation of SNP profiles will have social implications if these are used to suggest increasing likelihood of a person's ancestry and appearance, for example. As we shall see, forensic studies that attempt to provide the criminal justice system with strong leads to probable suspects are now being developed. Because phenotypical stereotypes of race have played a large role in such identification, we must first turn to the literature that sets the stage for the reemergence of race in molecular-biological clothing.

## Context and Content for Feedback Loops: Setting the Stage for the Reentry of Race

By the mid-1970s, it had become abundantly clear that there is more genetic variation *within* the most current common socially used categories of race than

*between* these categories.[23] The consensus is a recent development. For example, in the early part of the twentieth century, scientists in several countries tried to link up a study of the major blood groups in the ABO system to racial and ethnic groups.[24] They had learned that blood type B was more common in certain ethnic and racial groups that some believed to be more inclined to criminality and mental illness.[25] They kept running up against a brick wall, however, because there was nothing in the ABO system that could predict behavior.

In the United States, an increasing awareness has developed over the past two decades of the problem that blood from Americans of European ancestry (i.e., mainly white) tends to contain a greater number of antigens than blood from Americans of African or Asian ancestry.[26] African Americans and Asian Americans who receive blood from white donors are at a greater risk for hemolytic reactions than are whites who receive blood from Asian American or African American donors.

Here, we come to a fascinating intersection between the biological and social sciences. In the United States, not only do whites make up approximately 80 percent of the population, but also proportionally fewer African American and Asian Americans donate blood than do whites. This social fact has some biological consequences that, in turn, have some social consequences.

Approximately 400 red blood cell group antigens have been identified. These antigens have been classed into a number of fairly well-defined systems: the most well known are the ABO and Rh systems, but there are other systems such as P, Lewis, *MN,* and Kell (standard hematology texts note ten systems, including ABO and Rh).

The clinical significance of blood groups is that in the case of a blood transfusion, individuals who lack a particular blood group antigen might produce antibodies that react with that antigen in the transfused blood. This immune response to alloantigens (nonself antigens) can produce hemolytic reactions, the most serious being complete hemolysis (destruction of all red blood cells), which can be life-threatening. Once generated, the capacity to respond to a particular antigen is more or less permanent because the immune system generates "memory cells" that can be activated by future exposures to the antigen. For those who have chronic conditions that require routine blood transfusion, this aspect of the immune response is critical, because it increases the likelihood of future transfusion incompatibility. A clinical goal, therefore, is to minimize immune responses to antigens in transfused blood, in part because

a crisis (such as trauma surgery) might require transfusion of whatever blood is available, regardless of its antigen composition.

Most blood banks only test for ABO and Rh—the most common classification systems. Testing for the other systems is considered inefficient and increases the cost of blood. It is essential to minimize the antibodies against blood group antigens for everyone. However, the way in which blood typing is done puts members of racial and ethnic minorities at greater risk for the negative consequences of frequent transfusions. The term *phenotypically matched blood* basically means that it is possible to use the social appearances of race as a rough approximation (of likely antigens) to screen to minimize antibodies (along with ABO and Rh).

Transfusion therapy for sickle cell anemia is limited by the development of antibodies to foreign red cells.[27] In one important study, the researchers evaluated the frequency and risk factors associated with such alloimmunization, and obtained the transfusion history, red cell phenotype, and development of alloantibodies in 107 black patients with sickle cell anemia who received transfusions. They then compared the results with those from similar studies in fifty-one black patients with sickle cell disease who had not received transfusions and in nineteen non-black patients who received transfusions for other forms of chronic anemia.

Vichinsky and colleagues conclude that alloimmunization is "partly due to racial differences between the blood-donor and recipient populations."[28] True enough, this might not be race in any essentialist conception, but that is precisely the point. Race as social construction can and does have a substantial effect on how people behave. As noted above in the examples from highly varying rates of prostate and breast cancer among certain populations, an important arena for further scientific exploration and investigation is the feedback between that behavior and the biological functioning of the body.

This provides a remarkably interesting intersection. While the full range of analysts, commentators, and scientists—from postmodern essayists to molecular geneticists to social anthropologists—have been busily pronouncing "the death of race," for practical clinical purposes, the concept is being resurrected in the conflation of blood donation frequencies, by race. I want to make it clear that I am not trying to resurrect race as a social construct (with no biological meaning) any more than I am trying to resurrect race as a biological construct with no social meaning. Rather, I am arguing that when race is used as a stratifying practice (which can be apprehended empirically and systematically),

there is often a reciprocal interplay of biological outcomes that makes it impossible to completely disentangle the biological from the social. While that may be obvious to some, it is completely alien to others, and some of those others are key players in current debates about the biology of race.

## The American Anthropological Association Statement on Race

In May 1998 the American Anthropological Association issued its own statement on race.[29] It attempts to address the myths and misconceptions, and in so doing takes a corrective stance toward the folk beliefs about race. The statement strongly states the position that "physical variations in the human species have no meaning except the social ones that humans put on them." But casting the problem in this fashion gives the impression that the biological meanings that scientists attribute to race are biological facts, while the social meanings that lay persons give to race are either errors or mere artificial social constructions, and not themselves capable of feedback loops into the biochemical, neurophysiological, and cellular aspects of our bodies that, in turn, can be studied scientifically. The statement of the Anthropological Association is consistent with that of the UNESCO statement on race. However, by formulating the matter so that "it is *only* the social meanings that humans provide" implies that mere lay notions of race provide a rationale for domination, but have no other utility.

There is profound misunderstanding of the implications of a social constructivist notion of social phenomena. How humans identify themselves, whether in religious or ethnic or racial or aesthetic terms, influences their subsequent behavior. Places of worship are socially constructed with human variations of meaning and interpretation and use very much in mind. Whether a cathedral or mosque, a synagogue or Shinto temple, those constructions are no less real because one has accounted for and documented the social forces at play that resulted in such a wide variety of socially constructed places of worship.[30] Race as social construction can and does have a substantial effect on how people behave. One important arena for further scientific exploration and investigation is the feedback between that behavior and the biological functioning of the body. It is now appropriate to restate the well-known social analytic aphorism of W. I. Thomas, but to refocus it on human taxonomies of other humans: *if humans define situations as real, they can and often do have real biological and social consequences.*

## Molecular Genetics and the New Conflation of Race and Forensics

In 1993, a British forensic scientist published what is perhaps the first DNA test explicitly acknowledged to provide "intelligence information" along "ethnic" lines for "investigators of unsolved crimes." Ian Evett, of the Home Office's forensic science laboratory in Birmingham, and colleagues in the Metropolitan Police, claimed that their DNA test could distinguish between "Caucasians" and "Afro-Caribbeans" with an 85 percent probability of accuracy.[31]

Evett's work, published in the *Journal of Forensic Science Society,* draws on apparent genetic differences in three sections of human DNA.[32] Like most stretches of human DNA used for forensic typing, each of these three regions differs widely from person to person, irrespective of race. But by looking at all three, say the researchers, it is possible to estimate the probability that someone belongs to a particular racial group. The implications of this for determining for legal purposes who is and who is not officially a member of some racial or ethnic category are profound.

These new technologies have some not-so-hidden potential to be used for a variety of forensic purposes in the development and authentication of typologies of human ethnicity and race. A contemporary update of an old idea of deciding on "degree of whiteness" or "degree of Indianness" is possibly on us anew with the aid of molecular genetics. The Congress of the United States passed the Allotment Act of 1887, denying land rights to those Native Americans who were "less than half-blood." The U.S. government still requires American Indians to produce "Certificates with Degree of Indian Blood" to qualify for a number of entitlements, including being able to have one's art so labeled. The Indian Arts and Crafts Act of 1990 made it a crime to identify oneself as a Native American when selling artwork without federal certification authorizing one to make the legitimate claim that one was, indeed, an authentic ("one-quarter blood") Native American even well into the 1990s.

As noted above, it is not art but law and forensics that ultimately will impel the genetic technologies to be employed in behalf of attempts to identify who is authentically in one category or another. Geneticists in Ottawa, Canada, have been trying to set up a system "to distinguish between Caucasian Americans and Native Americans on the basis of a variable DNA region used in DNA fingerprinting."[33] In the spring of 2000, a representative in the state legislature of Vermont introduced a bill, H.0809, which "proposes to authorize the com-

missioner of health to develop standards and procedures for DNA-HLA testing to identify individuals who are Native Americans."[34]

In 1989, Virginia was the first state to pass legislation requiring all convicted felons (not just sex offenders) to provide blood samples for use in a state DNA database. In the next three years, several states followed the lead of Virginia, and in 1993, the FBI initiated a national DNA databank to link the DNA profiles of convicts across state jurisdictions. The Omnibus Crime Control Act of 1994 included a provision for coordinating DNA databank systems nationwide. Soon thereafter, the Department of Justice awarded nearly $9 million to state and city agencies to improve their DNA testing capacities and to encourage uniform standards.[35] As a direct result, all fifty states have adopted laws requiring "specified offenders to provide blood samples for forensic DNA testing."[36]

For practical purposes, the issue of the authentication of persons' membership in a group (racial/ethnic/cultural) has been brought to the level of DNA analysis. The efficaciousness of testing and screening for genetic disorders in risk populations that are ethnically and racially designated poses a related set of vexing concerns for the separation of the biological and cultural taxonomies of race.[37] The technology to use "SNPs on chips" to group, identify, categorize, and marginalize is with us, but it is still in its infancy. The Department of Energy awarded a contract to IBM in early 1998 to produce a chip that can hold more than eight times the amount of information available and permit analysis at more than ten times the speed now possible with current chip technology.[38]

## Population/Group Taxonomy and the Relevance to Debates on Germ-Line Intervention

The current discussions and debates about whether we should engage in or support research that might alter the germ line rarely address the eugenic potential that is a possible outcome. Because bioethicists do not tend to formulate ethical concerns along dimensions of group stratification or access to political power on the part of "groups of individuals," the discussion about the ethics of germ-line intervention for group differentiation and social stratification is rare. As just noted, when we increase our understandings of the human genetic code, we will be able to sort groups at higher and lower risk for certain diseases more systematically. Current risk figures indicate that Ashkenazic Jews are at highest risk for Tay-Sachs, Americans of North European descent are at highest risk for cystic fibrosis, Americans of Mediterranean descent are at high-

est risk for beta-thalassemia, Americans of West African descent are at highest risk for sickle cell anemia, and so the list goes on. (See Table 10.2.)

If we go back to the burden of disease argument and also note the funding levels available for research for these diseases, we come to some interesting conclusions regarding germ-line intervention. If technology permitted entry into the germ line to knock out either cystic fibrosis or sickle cell disease in an individual, that individual (or parent or guardian acting in behalf of that individual) might well make the individual choice—affirmed by the bioethicist's professional framing of individual choice. But a different order of ethical concern surfaces if we think about this more at the social and political levels and less at the individual level. We have seen how Zuni Indians are far more likely to have a different mutation for cystic fibrosis than are Caucasians. We have also seen how the genetic test for cystic fibrosis is aimed at the DF508, the mutation most likely to be found in those of Northern European ancestry. In an earlier section of this chapter, I provided historical and contemporary evidence that genetic disease research is most likely to be aimed at those diseases that have the most politically powerful constituencies or for which there is a strong profit motive in the biotechnology industry. With more research dollars going into the DF508 than into that mutation which appears more frequently among the Zuni, individual Caucasians may come to believe that they are making an individual decision about entering the germ line. Stepping back to another level of analysis, it is the social, political, and economic engines that are driving molecular biology down certain corridors and not others. To reduce this to individual decision making is to reconjure Veblen's concern for trained incapacity.

The larger point is that it would require political mobilization, or the profit motive, to get to such a place. This means that groups with less power, or fewer numbers, will not have their germ line as the subject of such intervention. At an earlier point in this chapter, I reported how the genetic test for the mutation for cystic fibrosis which is more common in whites has been developed and is available, while no such test has been developed for the Zuni CF mutation—even though the Zuni have nearly as high a rate of CF.

I am suggesting that even if in some utopian world germ-line intervention went forward evenly across all individuals who sought it out, there would be unanticipated eugenic outcomes *for different groups.* These outcomes are unanticipated precisely because the ethical framework for this debate has trained us to think primarily in terms of individuals. But individuals are at risk for genetic

disorders (for which there is targeted research) because they are part of a larger group which places them at higher risk for that disorder. An individual with North European ancestry may be at higher risk for cystic fibrosis, but when the genetic test for this particular mutation is developed (DF508), and then further research produces the potential for germ-line intervention for this particular mutation, it now becomes clearer that such interventions will affect the germ line of this group. In sharp contrast, there being no genetic test for the Zuni mutation for cystic fibrosis, and no research leading to potential germ-line intervention, there is no potential for such selective eugenics for this group.

This is the group element of the germ-line debate hidden from our view because we have tended to reify the individual and his or her germ line. While this might not be a sufficient reason for either curbing, stopping, or advancing germ-line interventions, it is certainly a topic worthy of more serious reflection and collective decision making (about germ-line intervention) than we have thus far heard coming out of the bioethicists' community. The notion of who decides for the individual when a group outcome is at stake is often advanced in the United States to trump any group decision making. But who decides for the individual is often already preempted by the decision made by biotechnology firms and the NIH and NSF funding decisions as to what gene disorders to research.

The differential impact of human molecular biological research on different groups is highlighted by the germ-line intervention potential because future generations of a particular group would be more affected than that of other groups. This is in turn a function of how much research is focused on the genetic conditions for specific population groups. A good example comes from the first few decades of research on the distribution of genetic disorders in the Chinese and Jewish populations. Although there are more than 1.5 billion Chinese, the major genetic textbooks citing "high frequency diseases" listed only three for the Chinese—while those same textbooks listed fifteen such disorders for the Jewish population.[39] The most likely explanation of this difference is the allocation of resources for the research that generated those figures, not the actual occurrence of gene disorders.

## Pharmacogenomics as the Harbinger of Germ-Line Intervention

In the past few years, the field of pharmacogenomics has begun to develop around the delivery of pharmaceuticals to specific population groups. The new pharmacogenomics asserts unequivocally that there are racial differences in the

way various races respond to certain drugs. Writing in *Science* in mid-October 1999, Evans and Relling claim that "all pharmacogenetic polymorphisms studied to date differ in frequency among ethnic and racial groups."[40] Whether or not this is based on thoughtfully controlled subject populations, this helps explain the recent announcement that the Food and Drug Administration has just given a provisional green light for a pharmaceutical company (NitroMed) to proceed to try to market "the first ethnic drug," BiDil. It is a drug for heart disease specifically designed for the African American population. Blacks are reported clinically to have higher blood pressure rates than whites and are twice as likely as whites to have heart failure. This opened the door to biotechnology companies seeking to develop and market specific drugs ethnically and even "racially." In early 2001, NitroMed developed a drug designed specifically for African Americans.

It is not much of a conceptual leap from a pharmaceutical designed for a particular population group and a germ-line intervention designed for such a group. Yet, since economic profit will drive the engine of biotechnology (unashamedly, proudly pronounced as the sine qua non of good business in a capitalist society), a germ-line intervention for the Zuni is not in the cards—or perhaps, more realistically, not in the profit margin.

There are always those who would assert that this development does not constitute a difference in kind from any other health intervention, because the wealthier and the more powerful usually have greater access to health interventions from all kinds of technologies. However, this would miss the key purpose of this essay, which has been an attempt to help reframe the debate and focus more attention on the subterranean eugenic potential of interventions to the germ line *for population groups*—a dimension that I hope can now be seen as different in degree and in kind from discussions that have focused on the bioethics of individual decision making about the germ line. The eugenic potential of germ-line intervention on communities and groups of various shapes and dimensions is hidden precisely because of this overly determined professional focus on individual decisions.

## NOTES

1. J. Hector Pope, Tom P. Aufderheide, Robin Ruthazer, Robert H. Woolard, James A. Feldman, Joni R. Beshansky, John L. Griffith, and Harry P. Selker, "Missed Diagnoses of Acute Cardiac Ischemia in the Emergency Department," *New England Journal of Medicine* 342 (April 19, 2000): 1163–70.

2. Ralph Nader, a famous graduate of Harvard Law School, was once invited back

to give the commencement address. "I know about legal training," said Nader, "like honing a pencil, they make you sharp by making you narrow."

3. John A. Robertson, *Children of Choice: Freedom and the New Reproductive Technologies* (Princeton: Princeton University Press, 1994), 23.

4. Ibid., 22.

5. James H. Jones, *Bad Blood: The Tuskegee Syphilis Experiment—A Tragedy of Race and Medicine* (New York: The Free Press, 1981).

6. In June 1957, the *American Journal of Obstetrics and Gynecology,* the leading scientific journal for practitioners in those fields, printed an advertisement (14) that "recommended Diethylstilbestrol (DES) for routine prophylaxis in ALL pregnancies." The advertisement cited empirical research in one series of 1,200 patients, and proudly pronounced that in this series, 96 percent of the women had "bigger and stronger babies, too. No gastric or other side effects with desPLEX—in either high or low dosage."

7. Diethylstilbestrol (DES) residues were detected in beef and sheep livers assayed in 1972 and 1973. When diethylstilbestrol was used to enhance the growth of sheep and cattle, a substantial portion of the U.S. population was exposed to potentially toxic levels in beef and mutton.

8. Things can get complicated when it comes to adults speaking for minors or for those judged to be mentally incapable of speaking for themselves. But this is nothing in contrast to trying to discern who speaks for the group. Who speaks for mentally ill persons, for example, was the source of a long-standing forty-year struggle chronicled by Susan Chandler (Susan Meyers Chandler, *Competing Realities: The Contested Terrain of Mental Health Advocacy* [New York: Praeger, 1990]). In the beginning, professionals such as psychiatrists and psychologists spoke in behalf of mentally ill persons. A movement ensued in which the family caregivers asserted greater rights. And then in the last two decades of the twentieth century, mentally ill persons came forward "to speak for themselves" in increasing numbers. Thus, in this complicated world of ethical deliberations, we see the beginning contours of the problem of who is entitled to make decisions for others.

9. The exception being if one is part of a politically or economically powerful group. See the discussion immediately below.

10. Adele E. Clarke and Joan H. Fujimura, eds., *The Right Tools for the Job: At Work in Twentieth-Century Life Sciences* (Princeton: Princeton University Press, 1992); and Steven Epstein, *Impure Science: AIDS, Activism, and the Politics of Knowledge* (Berkeley: University of California Press, 1996).

11. R. B. Scott, "Health Care Priorities and Sickle Cell Anemia," *Journal of the American Medical Association* 214, no. 4 (1970): 731–34.

12. Philip Reilly, *Genetics, Law and Social Policy* (Cambridge, Mass.: Harvard University Press, 1977), 79–83.

13. The following segment is based on materials in my chapter, "The Social Consequences of Genetic Disclosure," in *Behavioral Genetics: The Clash of Culture and Biology,* ed. Ronald Carson and Mark Rothstein (Baltimore: Johns Hopkins University Press, 1999).

14. Segments of this chapter are excerpted from Troy Duster, *Backdoor to Eugenics* (New York: Routledge, 1990).

15. This is a rate that is unprecedented, according to demographers who have been tracking such statistics around the world. The size of the "loophole" mentioned refers

to the fact that the 1994 law in India focused on clinics only. In fact, ultrasound machines are used, and these machines are portable. Mobile units, buses, or even trucks can go into the rural areas, where nearly 80 percent of the Indian population lives, and avoid the whole issue of clinic control. ("India Fights Abortion of Female Fetuses," *New York Times,* August 27, 1994.)

16. "China's Misconception of Eugenics," *Nature* 367, no. 1 ( January 6, 1994).

17. Ibid. This refers to a development that was reported in the *New York Times* (November 14, 1993) entitled "China to Ban Sex-Screening of Fetuses." Health Minister for China Chen Minzhang announced the plan to enforce a new law that would not only prohibit screening of the fetus for sex determination but also ban marriages for people "diagnosed with diseases that may totally or partially deprive the victim of the ability to live independently, that are highly possible to recur in generations to come and that are medically considered inappropriate for reproduction."

18. Stephanie E. Clipper, *Huntington's Disease: Hope through Research* (Bethesda, Md.: Office of Scientific and Health Reports, National Institute of Neurological Disorders and Stroke, 1998).

19. Per Jensen, Kirsten Fenger, Tom G. Bolwig, and Sven Asger Sorensen, "Crime in Huntington's Disease: A Study of Registered Offences among Patients, Relatives, and Controls," *Journal of Neurology, Neurosurgery, and Psychiatry* 65 (1998): 467–71.

20. Ibid., 468.

21. In September 1992, the March of Dimes published results of their study, a Lou Harris poll entitled "Genetic Testing and Gene Therapy." The study summarized findings of a national survey of attitudes of the U.S. population about the new genetic technologies, and found the overwhelming majority of Americans (more than seven in ten) strongly favored genetic therapy. This of course presumed that one could locate "the gene for" and then provide therapeutic intervention.

22. L. Luca Cavalli-Sforza, in *Plain Talk about the Human Genome Project,* ed. Edward Smith and Walter Sapp (Tuskegee, Ala.: Tuskegee University, 1997).

23. Anthony P. Polednak, *Racial and Ethnic Differences in Disease* (New York: Oxford University Press, 1989); A. H. Bittles and D. F. Roberts, eds., *Minority Populations: Genetics, Demography and Health* (London: Macmillan, 1992); Malcolm Chapman, ed., *Social and Biological Aspects of Ethnicity* (New York: Oxford University Press, 1993); Pat Shipman, *The Evolution of Racism: Human Differences and the Use and Abuse of Science* (New York: Simon and Schuster, 1994).

24. William H. Schneider, "The History of Research on Blood Group Genetics: Initial Discovery and Diffusion," *History and Philosophy of the Life Sciences* 18, no. 3 (1996): 277–303. (For the discussion in this paragraph and for the references to the German literature which are used here, I am indebted to William H. Schneider.)

25. Max Gundel, "Einige Beobachtungen bei der rassenbiologischen Durchforschung Schleswig-Holsteins," *Klinische Wochenschrift* 5 (1926): 1186; G. A. Schusterov, "Isohaemoagglutinierenden Eigenschaften des menschlichen Blutes nach den Ergebnissen einer Untersuchung an Straflingen des Reformatoriums (Arbeitshauses) zu Omsk," *Moskovskii Meditsinksii Jurnal* 1 (1927): 1–6.

26. E. P. Vichinsky, A. Earles, R. A. Johnson, M. S. Hoag, A. Williams, and B. Lubin, "Alloimmunization in Sickle Cell Anemia and Transfusion of Racially Unmatched Blood," *New England Journal of Medicine* 322 ( June 7, 1990): 1617–21.

27. Ibid.

28. Ibid.

29. This statement, approved by the Executive Board on May 17, 1998, can be found at www/ameranthassn.org/racepp.htm.

30. Joan Fujimura, "Authorizing Knowledge in Science and Anthropology," *American Anthropologist* 100 ( June 1998): 347–60.

31. I. W. Evett, J. S. Buckleton, A. Raymond, and H. Roberts, "The Evidential Value of DNA Profiles," *Journal of the Forensic Science Society* 33 (1993): 243–44.

32. I. W. Evett, "Criminalistics: The Future of Expertise," *Journal of the Forensic Science Society* 33 (1993): 173–78.

33. "Genes in Black and White," *New Scientist* ( July 8, 1995): 34–37.

34. The title of the bill is An Act Relating to DNA Testing and Native Americans Sec. 1. 18 V.S.A. §104( j) was added to read: "( j) The commissioner shall by rule establish standards and procedures for DNA-HLA testing to determine the identity of an individual as a Native American, at the request and the expense of the individual. The results of such testing shall be conclusive proof of the Native American ancestry of the individual."

35. Fox Butterfield, "U.S. Has Plan to Broaden Availability of DNA Testing," *New York Times,* July 14, 1996.

36. Dorothy Nelkin and Lori Andrews, "DNA Identification and Surveillance Creep," *Sociology of Health and Illness* 21, no. 5 (1999): 689–706.

37. In New York City, Mayor Rudolph Guiliani was an advocate for the use of DNA testing of those arrested by the police. He has been joined by others, who convinced Attorney General Janet Reno that she should appoint a commission to bring back recommendations on this matter. The report was completed in December 2000, and concluded that such data collection would pass constitutional muster. Critics have pointed to the fact that who the police stop and arrest is not a neutral matter, but heavily politically biased, and in particular, racially biased. Indeed, the American Civil Liberties Union has filed a lawsuit to stop the police from targeting primarily African Americans.

38. For an excellent summary of the promise and limits of the new gene chip technology, see Hisham Hamadeh and Cynthia A. Afshari, "Gene Chips and Functional Genomics," *American Scientist* 88 (November–December, 2000): 508–12.

39. Duster, *Backdoor to Eugenics,* 160–62, note 14.

40. William E. Evans and Mary V. Relling, "Pharmacogenomics: Translating Functional Genomics into Rational Therapeutics," *Science* 286 (October 1999): 487–91.

CHAPTER ELEVEN

# Ethical Differences between Inheritable Genetic Modification and Embryo Selection

Bonnie Steinbock, Ph.D.

Germ-line gene therapy, or inheritable genetic modification (IGM), offers the possibility of preventing serious genetic disorders by replacing defective genes in an embryo with functioning genes. Thus, IGM might be able to treat genetic disease in the embryo, instead of the current method of prenatal diagnosis and selective abortion. In avoiding the need for abortion, IGM resembles preimplantation genetic diagnosis (PGD). PGD is a technique to determine genetic defects in embryos created by in vitro fertilization (IVF) before implantation in a uterus for gestation. The diagnosis occurs at the six- to ten-cell stage of embryonic development, when one or two cells can be removed without harming the embryo or affecting its potential to implant. The cellular DNA is then tested for chromosomal abnormalities or genetic mutations, using polymerase chain reaction (PCR) for monogenic diseases and fluorescent in-situ hybridization (FISH) for chromosomal aberrations.[1] Embryos carrying serious genetic diseases are discarded (or frozen indefinitely); embryos free of disease can be implanted for gestation.

Because embryos are discarded before implantation, PGD obviates the need for prenatal testing and abortion. Whether this makes PGD morally superior

to abortion depends on one's view of the moral status of the embryo and fetus. Those who regard fetuses as having greater moral value or status than preimplantation embryos will regard PGD as morally superior to abortion. Those who regard even early embryos as human persons will not. Indeed, from the perspective of loss of prenatal life, PGD is *worse* than traditional prenatal diagnosis and selective abortion, because PGD requires the creation of numerous embryos for each live birth produced.[2]

IGM differs from PGD (and obviously abortion) in that it does not involve embryo selection or discard (much less, killing a fetus). Thus, IGM avoids the entire issue of the moral status of the embryo. In addition, many find the idea of IGM attractive because it "fixes" rather than discards embryos. Walters and Palmer argue that gene therapy is preferable to embryo selection because it "best accords with the health professions' healing role." They write: "prenatal diagnosis followed by selective abortion and preimplantation diagnosis followed by selective discard seem to us to be uncomfortable and probably discriminatory halfway technologies that should eventually be replaced by effective modes of treatment."[3]

A problem with both IGM and PGD is that they require the creation of extracorporeal embryos, embryos created through IVF. This means subjecting the woman to drugs which cause her to superovulate, and which have significant side effects, including bloating, weight gain, fatigue, hot flashes, depression and mood swings, and possibly an increased risk of ovarian cancer.[4] IVF not only poses significant health risks to the woman, but also is less likely to result in a successful pregnancy and is of course more expensive (and less fun) than making babies the old-fashioned way. For these reasons, PGD might be appropriate for infertile couples already undergoing IVF who are at risk of passing on a genetic disease, but it is not clear that it would be advisable for fertile couples. This would depend on how strongly they were opposed to selective abortion and how strongly they wished to avoid having a child with a genetic disease.

The alleged advantage of IGM is that it cures the disease instead of discarding the embryo. However, in virtually all genetic diseases, the risk of transmission is not 100 percent. This means that both affected and unaffected embryos will be created using IVF, and PGD would be needed to discover which of the embryos had the genetic defect in question. But as one critic of germ-line gene therapy has asked, why would it make sense to attempt to correct an embryo with a genetic defect? "Surely one should discard the affected and reimplant

one of the unaffected."[5] IGM would make sense only if the number of embryos created by IVF were limited to the number that would be transferred. In that case, there would be a point to fixing a defective embryo so that it could be transplanted. However, it would obviously be simpler and less expensive to follow the standard practice of creating more embryos than can be transplanted and choosing the unaffected ones for implantation.

In any event, unless IGM were foolproof, selective abortion might not be avoided after all. Couples undergoing PGD at present are advised to have prenatal diagnosis "just in case," and thus may have to face the abortion decision after all. The same would likely be true for those who opt for curing embryos of genetic disease via IGM. This makes the decision process of the couple considering gene therapy very "iffy": on the one hand, they may say to themselves, if the gene therapy works, and we don't know how likely that is, then we could have a child without a genetic disease without resorting to abortion and "trying again." On the other hand, if it does not work, we are faced with the choice of abortion or raising a child with a serious genetic disease. Moreover, there are unknown risks of harmful unintended effects gene intervention could impose on offspring. It is not clear how couples would be counseled in the face of such uncertainty, or what would count as a rational decision.

The major use of PGD in recent years in the United States has been to increase the efficacy of IVF.[6] Some 50 to 70 percent of embryos created through IVF have chromosomal abnormalities, presumably a major factor in the low rates of pregnancy for IVF. If these embryos can be identified and discarded, the chances of having a successful pregnancy and a take-home baby are improved. Increasingly, then, in the United States, PGD is becoming an adjunct to IVF, rather than the other way around. In the United Kingdom, the Human Fertilization and Embryology Authority (HFEA) approved the screening of embryos for chromosomal abnormalities in 2001. It was the first time that the authority had approved a technique that detects a range of genetic abnormalities rather than one specific genetic disease. The authority was criticized by Human Genetics Alert, a group that monitors developments in genetic medicine, on the ground that this crosses "the crucial ethical line between testing individuals for specific genetic disabilities and a broad screening program."[7] The group accused the authority of introducing a screening program for Down syndrome and other disabilities "by stealth." Paul Tully, of the Society of the Protection of Unborn Children, characterized aneuploidy screening as a slippery slope. "We are starting to eliminate those with more manifest 'imperfec-

tions' through this procedure and it may well move on to other conditions, such as heart disease or breast cancer. These arguments are going to be very difficult for society to go back on once they have approved the principle."[8]

The HFEA justified its decision by saying, "An embryo that is aneuploid contains an abnormal number of chromosomes and usually results in a failure to implant or may miscarry. Screening for aneuploidy can benefit in particular those women who have suffered repeated miscarriage or IVF failure by identifying embryos that are most likely to successfully implant."[9] It is hard to see how screening embryos for defects that will prevent them from implanting gets us onto a slippery slope. The arguments from disability advocates and pro-lifers seem based on the misconception that the embryos, if not screened and discarded, could have had a chance at life, albeit with a disability. While this argument does not make sense when screening is used to prevent miscarriage, it is an argument that needs to be taken seriously in the context of genetic screening generally. Many disability advocates (and others) are suspicious that the real goal in screening is to prevent the births of people who have disabilities. Dr. Richard Nicholson, editor of the *Bulletin of Medical Ethics,* says, "We are now moving rapidly into an age of saying there are lives that are not worth living, and we either prevent them by abortion if they are discovered ante-natally, or we now are moving into the hi-tech way of pre-conceptional prevention." Nicholson called this "the Nazification of medicine."[10]

## The Disability Critique

Disability rights is the latest form the civil rights movement has taken. Like race and gender, disability is no longer a permissible basis for discrimination. But rights movements often go beyond nondiscrimination. Skin color, race, ethnic identity, gender, and sexual orientation are often viewed as a source of identity and pride. Identity politics has a special resonance for people with disabilities precisely because of the possibility of "fixing" disability. The prevalent view of disability, one that is rejected by the disability critique, is the medical model. It maintains that disability is primarily a medical problem, and one that it is desirable to fix or cure by medical means.

By contrast, the perspective favored by disability rights advocates is a sociopolitical model, which focuses on social institutions and arrangements as being the problem or the solution to the problem. They argue that it isn't so much the disability that makes life difficult for people with disabilities, but so-

ciety's reaction to disability. Disability activists focus on changing society, rather than curing disability.

The medical model view was portrayed on an episode of "ER," when Dr. Benton talked with a deaf physician about his hearing-impaired child. Dr. Benton wanted to get the child cochlear implants so that he could hear. The deaf physician suggested that he ought to come to terms with his son's deafness and get him instruction in sign language. She argued that being deaf is like being black: part of his son's identity. Dr. Benton said that being deaf is a medical condition and he wanted a medical cure. The deaf (sometimes written "the Deaf") are particularly attracted to the notion of deafness as providing identity, because they have their own language, which gives rise to their own culture. Many deaf people oppose cochlear implants, not merely because they often do not work too well, but because they think that sign language is just as good as spoken language. Many deaf people say that they would not want to be hearing, even if it were possible. (As one put it, "Why would I want all that noise?") Some disability rights advocates apply this model to all disability. Some of them criticized Christopher Reeves, the actor who was rendered quadriplegic in a riding accident, for expressing a desire to walk again. This was seen as a betrayal of the disability community.

In my opinion, this is an extreme and unacceptable position. Of course, society can and should do more to accommodate those with disabilities, but it should also do what it can to prevent and cure disability. The reason is that disability limits people, even in a perfectly accommodating society. This is acknowledged by sensible disability rights advocates, such as Adrienne Asch, who writes: "Not all problems of disability are socially created and, thus, theoretically remediable. . . . The inability to move without mechanical aid, to see, to hear, or to learn is not inherently neutral. Disability itself limits some options. Listening to the radio for someone who is deaf, looking at paintings for someone who is blind, walking upstairs for someone who is quadriplegic, or reading abstract articles for someone who is intellectually disabled are precluded by impairment alone. . . . It is not irrational to hope that children and adults will live as long as possible without health problems or diminished human capacities."[11]

Disability advocates like Asch do not object to attempts to prevent or cure disability, so long as this does not preempt attempts to make society more open and accessible to those who have disabilities. However, many distinguish between preventing disability in an existing or future individual, which they re-

gard as permissible, and preventing the existence of individuals who are or might become disabled, which they reject. Under the first category would come putting folic acid in flour to protect future children from developing spina bifida. Under the second category would come prenatal screening for spina bifida and aborting affected fetuses. This is not protecting the health of unborn children, but rather killing them.

While many disability activists are pro-choice, and do not object to abortion per se, they do object to aborting fetuses simply because they have, or will have, or may have, a disability. Asch compares this to aborting fetuses because they are the "wrong" sex.[12] On Asch's view, it is morally permissible to abort a pregnancy if you don't want a child. It is not morally permissible to abort because you don't want *this* child, because of some feature the child has. Abortion for fetal indications is usually chosen, she argues, for the following two reasons. First, prospective parents know very little about what life with a disabled child is like. If they knew more about what individuals with that disability can be and accomplish, they would be much less likely to resort to aborting a wanted child. Second, the very possibility of prenatal screening leads parents to expect a "perfect baby," and to be unwilling to "settle" for less. Thus, prenatal screening is held to increase intolerance of imperfection, and thus it increases discriminatory attitudes toward disability. Asch objects to PGD and embryo selection on the same grounds as she objects to prenatal screening and selective abortion.[13] Both get rid of a wanted child on the basis of only one of its (presumed) traits.

Elsewhere I have argued against Asch that it is not objectionably perfectionist, but perfectly reasonable of prospective parents to want a healthy, disease-free baby.[14] I have also argued that PGD and even selective abortion can be viewed as forms of prevention, at least by those who do not think that embryos and fetuses are equivalent to babies. Asch is pro-choice. She thinks that women should be able to have abortions because having a child would impose significant burdens, such as forcing a hiatus in a woman's education or career. However, having and raising a child with a serious disease can be equally burdensome. If abortion is justified in the one case, I do not understand why it is not equally justified in the other. And only the woman facing the pregnancy is in a position to decide whether she wishes to undertake the burdens and challenges involved.

Although both abortion and PGD can be seen as methods of prevention, they are not psychologically or morally identical. Abortion is usually fairly

traumatic when it terminates a wanted pregnancy. By contrast, couples are unlikely to experience distress at discarding preimplantation embryos that have genetic defects. This is a reason for preferring PGD to abortion. I do not think the same argument applies to the comparison between PGD and IGM. Both can be seen as forms of prevention, and IGM is not necessarily superior to PGD. Indeed, as I have pointed out, PGD is likely to be a more effective and less expensive method of preventing genetic disease.

Some people are opposed in principle to any manipulation of the germ line, no matter how safe or effective, even for purposes they accept as morally acceptable. For example, the Council for Responsible Genetics in a publication entitled, "Say No to Designer Children," writes: "Of all the issues arising from genetic engineering, the threat of germ-line manipulation is perhaps the most ominous. The Council for Responsible Genetics (CRG) strongly opposes any attempt to change future generations through genetic engineering." CRG opposes any therapy that might affect, even unintentionally, the germ line because, as CRG board member and developmental biologist Stuart Newman explains, "We must not accept a mindset that would subject human beings to manufacturing technologies and eventually lead to designer children." CRG regards IGM as ushering in a Brave New World envisioned by Aldous Huxley in the 1930s and taking us farther down the slippery slope to eugenics, in which any child who doesn't measure up to some arbitrary standard of health, behavior, or physique is seen as flawed.

This sounds quite similar to anti-eugenic arguments mounted by disability activists. Yet there is a significant difference between the two groups. CRG says that IGM is "simply not needed, as parents concerned about passing on a gene mutation to their children have a number of safe alternatives, including *carrier screening, prenatal testing* and adoption" (my emphasis). As we have seen, many disability rights activists draw a sharp distinction between therapy that can cure or prevent genetic disease in an existing individual, which they do not in general oppose, and embryo or fetus selection, which they do. They regard prenatal testing which can prevent passing on a gene mutation only through embryo selection or abortion as an unacceptable alternative. My own view is that both prenatal testing and genetic modification are in principle acceptable, although the pragmatic reasons against IGM seem very strong.

There is one more concern that has been voiced about both IGM and PGD. It is that these techniques could be used, not to prevent miscarriage or even to prevent serious genetic diseases, but that they could be used in the attempt to

get a "perfect baby." PGD can be used not only to prevent miscarriage or the birth of a baby with a genetic disease; it has also been used by a New York couple to help them have a baby free of Li-Fraumeni syndrome, a genetic condition caused by a mutation in the p53 gene, which the father has. People with the syndrome have about a 50 percent chance of getting cancer by age forty and a 80 to 90 percent lifetime cancer risk—about double the standard 40 percent risk. The question, then, is whether this degree of risk justifies embryo screening. Moreover, some wonder whether we will begin testing for even more remote risks and less harmful conditions. "The technology has freed a growing number of families from the ancestral chains of inherited illness, but it has also raised fears that parents may soon be able to choose from a menu of less-pressing genetic traits, heralding an age of 'designer babies.'"[15]

It seems to me that Li-Fraumeni syndrome is not a trivial condition, and that prospective parents should be able to decide for themselves whether the risk of the disease warrants PGD. After all, if the disease can be detected prenatally, the decision whether to terminate would certainly belong to the parents. Why, then, should we be more concerned about the decision to prevent it preconceptionally?

The real concern, I think, is not with disease at all, but rather the prospect that we will one day be able to have children "to spec": that we will be able to determine their coloring, height, weight, intelligence, personality, athletic ability, and so forth. It would be the crudest sort of genetic determinism to think that parents would be able to "design" their children. Traits like intelligence, athleticism, or musical talent most probably involve many genes, making it extremely unlikely that IGM could produce a genius. Moreover, we cannot forget the role of the environment. At the same time, if IGM were available, people who could afford it might use it to give their child a genetic edge. Others in this volume have addressed this issue and, as it goes beyond the scope of my topic, I will not attempt to discuss it here. However, I will note that the prospect of "designer babies" seems to be more of a threat from IGM than from PGD and embryo selection, since IGM—if ever perfected—would allow for introducing traits, not just discarding embryos with defects.

## Conclusion

Both PGD and IGM are methods of preventing the births of people with genetic diseases. IGM has the advantage of "curing" rather than discarding em-

bryos, and thus seems more in keeping with the medical mission. However, IGM may have unforeseen side effects that would make it too risky to be attempted. In any event, given that we would have to use PGD to identify which embryos needed fixing, it is hard to see why we would not simply discard such embryos and implant only unaffected ones. While both PGD and IGM can be seen as forms of prevention, the pragmatic reasons in favor of PGD seem overwhelming.

NOTES

1. W. Lissens and K. Sermon, "Preimplantation Genetic Diagnosis: Current Status and New Developments," *Human Reproduction* 12 (1997): 1756–61.

2. J. R. Botkin, "Ethical Issues and Practical Problems in Preimplantation Genetic Diagnosis," *Journal of Law, Medicine and Ethics* 26 (1998): 17–28.

3. L. Walters and J. G. Palmer, *The Ethics of Human Gene Therapy* (New York: Oxford University Press, 1997), 82.

4. M. A. Rossing, J. R. Daling, N. S. Wiess, D. E. Moore, and S. G. Self, "Ovarian Tumors in a Cohort of Infertile Women," *New England Journal of Medicine* 331 (1994): 771–76.

5. D. M. Danks, "Germ-Line Gene Therapy: No Place in Treatment of Genetic Disease," *Human Gene Therapy* 5 (1994): 151–52.

6. E-mail communication from Jeffrey R. Botkin.

7. A. Ferriman, "UK Approves Preimplantation Genetic Screening Technique," *British Medical Journal* 323 (2001): 125.

8. B. Marsh, "'Perfect Baby Soon' as Genetic Test is Approved," *Daily Mail,* November 12, 2001.

9. Ferriman, "UK Approves Preimplantation Genetic Screening Technique."

10. BBC Online Network (1999), "Health Warning over 'Nazi' Genetic Screening."

11. A. Asch, "Reproductive Technology and Disability," in *Reproductive Laws for the 1990s,* ed. S. Cohen and N. Taub (Clifton, N.J.: Humana Press, 1988), 73.

12. Ibid., 69–124.

13. Although Asch obviously could not discuss PGD in her 1988 paper, she made her opposition to PGD as a form of prenatal testing clear in a 1996–98 Hastings Center working group on Prenatal Testing for Genetic Disability.

14. See my "Disability, Prenatal Testing, and Selective Abortion," in *Prenatal Testing and Disability Rights,* ed. Erik Parens and Adrienne Asch (Washington, D.C.: Georgetown University Press, 2000), 108–23.

15. R. Weiss, "Gene Tests Allow Disease-free Baby," *Washington Post,* June 9, 2001.

CHAPTER TWELVE

# Human Limits

## Theological Perspectives on Germ-Line Modification

Ronald Cole-Turner, Ph.D.

The prospect of technologies of human self-modification evokes intense religious responses. Religious convictions, even if poorly articulated or conflicted, form the deep ground of popular sentiment from which explicit policy options emerge. Anyone engaged in serious analysis of science policy will be helped by a greater understanding of these religious convictions and the assumptions on which they depend. In this chapter I try to uncover some of the most important religious convictions that bear on these technologies. I see this as a contribution of theology to a broader public discussion.

Theology contributes best, I believe, when it recognizes the pluralistic and secular nature of our society, and therefore not when it offers answers, much less insists that its answers become law, but when it invites citizens of every perspective and persuasion to reflect on the nature and meaning of human life in its many relationships and possibilities. Religious institutions contribute most when they create an open space in society for serious, critical, and sustained attention to such issues. Indeed, it is precisely the lack of deep reflection that religion wants most to challenge and correct. From a religious perspective it is worrisome that we human beings may soon cross such an important threshold

into an era of germ-line or inheritable genetic modifications without deep pause, that we might do so in private clinics acting without public review, or that we might do so inadvertently. By sharing its worries, theology invites us all to push back for a moment from the immediate practicalities of gene modification or disease pathways to the deeper questions of cultural and spiritual modification and human evolutionary pathways.

Despite its reputation theology is not esoteric. Its questions are often ordinary questions taken one step further than usual. The central question for our consideration is whether human inheritable genetic modification would violate a fundamental human limit. Theology takes the question to its ultimate level, asking whether such technological intervention violates our creaturely limits by somehow offending against our relationship with our creator. But we encounter this question of limits at many points before this ultimate stage. For instance, among human limits are the obvious limits of human knowledge. We may not now understand a certain process, or we may be limited by our lack of knowledge of a natural system in its full complexity, which is certainly the case now when we contemplate the genetic and cellular complexity of our own brains. Theologians of various traditions, especially Christianity, have stressed the need for great modesty about human knowledge.

Perhaps more important, they (together with philosophers as far back as Plato) have stressed the importance of self-knowledge and its limits. Do we really know ourselves? Do we deceive ourselves, thinking we are morally or intellectually better than we really are, or that we are less self-transparent than we like to think? Are we each not in fact a conflicted set of motivations and aspirations, wanting this and that, wanting good and selfish ends, wanting to be good but only partly wanting it, all the while deluding ourselves about the purity or coherence of our purposes, and thus limited in respect to our clarity of purpose?

We are also confronted by technical limits. Of course, technology advances, and so the tight squeeze of today's technical limitations is pushed back again and again, and each time our moral analysis must take account of our new circumstance. Current limitations in somatic cell modification, vectors, and the ability to act early in developmental processes all affect our analysis of what is morally permissible. For example, some religious people might argue that a therapeutic abortion is permissible in a situation of a serious disease as long as we cannot effectively treat the disease. As technology changes, duties and morally permissible options change. If successful, techniques of human germ-

line modification would push back significant limits on our ability to treat certain conditions. On the other hand, in thinking about technical limitations, we must distinguish between the technical ability to change a causal element (such as a DNA sequence) and the ability to control an outcome. As we push back the limits on our ability to alter genes, we need clarity about the remaining limits on our ability to control outcomes in complex systems, such as the gene/environment interactions or the life experience of the affected individuals. Excessive confidence about our ability to control one part of a system might blind us to our limited ability to control another, much less to determine the system as a whole. Nevertheless, religious people often express the conviction that it is a religious duty to pursue research in order to push back the current limits of our healing powers, saying that if it is possible in the future to treat certain diseases, we have the obligation to learn how.

We are also limited by the accidents of our biology and by the results of our own evolution: we can walk but cannot fly; we can see light but not other forms of energy; and our brains, evolved to see food but avoid becoming food, are selective in their ability to process information. We are limited in life span, vigor, and resistance to disease and parasites. We turn to technology to help us surmount such limits, and in many ways our technology helps, but always within new limits. Now, however, we face a wholly new prospect. In the past our technology has aimed at compensating for our biological/evolutionary/genetic limits, not at removing them. But now we are beginning to acquire the technology to alter not just our environment but our genes, and so the question now becomes whether it is right to use technology to surmount some genetic limits. There is widespread agreement that we should, for instance, use genetic technology to treat clear-cut cases of genetic disease using somatic cell gene transfer or modification. Doing so, we think, does not violate any limit because it involves bringing a person, who is ill, into the normal range for the species. People of religious conviction appear to share this view; that is, they tend to see somatic cell gene therapy as merely an extension of previous medicine, morally speaking.

But are we limited to acting within the normal range for our species? Or are we limited to acting upon those who can give consent and prohibited from acting on future generations, for instance, through germ-line modification? For many people, the removing of human genetic limits at this level is a crossing or a violation of moral limits that should constrain our technology. Some are especially troubled by germ-line modification because they fear a certain self-

destructive illogicality implicit in its program. This fear may be summarized, first, by the phrase *designer children.* Designer children, it may be argued, are engineered, contrivances of the will, artifacts of human action, and *therefore* not human themselves, at least not in respect to the relationship they should have with parents. Although ever so slightly, the genetic basis of their existence has been compromised in respect to its being free of human artifice. Will subverts being, not because the designer either harms or improves the designed, but because designed and designer cannot be persons in mutual relationship. They are destined forever to be engineer and artifact. A designed child is not a child at all, for being a child implies having a relationship with parents. A designed person is not a person in the fullest sense, for being a person is possible only as person-in-relationship to other persons. The designed person is a product of a technology in the service of a human will that ignores an intrinsic limit imposed by the logic of persons: if I design you, you are to me not a *you* but an *it.*

Second, and in a more distant time frame, this fear may be summarized by the word *transhuman.* Consider the somewhat fanciful comments of Lee Silver, who may be engaging in hyperbolic flights of imagination but who nonetheless provides a useful counterpoint to our reflection. Referring to a time about two centuries from now, he writes: "It was a critical turning point in the evolution of life in the universe. . . . Throughout it all, there were those who said we couldn't go any further, that there were limits to mental capacity and technological advances. But those prophesied limits were swept aside, one after another, as intelligence, knowledge, and technological power continued to rise."[1] Notice how *limits to mental capacity* are themselves pushed back by technology, making even better technology possible. By improving genes, we improve our children's ability to improve their children's genes. In this way, technology ratchets evolution forward on a fast-track, so that mere millennia replace aeons in achieving evolutionary "progress." Future generations are better engineers because they are the results of better engineering.

Silver continues with his speculations, now referring to a time more than a millennium away: "A special point has now been reached in the distant future. And in this era, there exists a special group of mental beings. Although these beings can trace their ancestry back directly to *homo sapiens,* they are as different from humans as humans are from the primitive worms with tiny brains that first crawled along the earth's surface."[2]

If we use germ-line modification as Silver suggests and improve ourselves to

the point of species-transcendence, we will by definition have destroyed ourselves. Or if not, that is, if we will have left some of our descendants unaltered to live among our improved-but-no-longer-human progeny, those like us will serve, envy, rebel against, and perhaps even worship the improved. Or will they worship us, their creators? And if we succeed in the dream of some in genetics research and achieve a significant increase in human longevity so that the unmodified old live side by side with their much improved descendants, we will have created multiple generation gaps, even chasms. More important, here we confront a limit implied by the meaning of species, a limit not so much biological as logical. If we transcend our species, will *we* still exist? Should we ignore this limit and transcend our kind? Should some of us decide for humanity? Will *they* (our transhuman progeny) approve?

These various forms of limits—limits of knowledge, technique, personhood, nature, and species—confront us whether we are religious or not. Do they point to a moral line that must not be crossed? And would *any use* of germline modification cross such a line and thus be impermissible? Perhaps not. In fact, I would suggest that careful, constrained efforts at intentional germ-line modification would not violate the limits we have discussed so far. In suggesting this, I note that of all these limits discussed so far, the most troublesome may turn out to be what I have called the "logic of persons," for even the most careful and constrained uses of germ-line modification would bring into existence "persons" who will relate to others, not as their parents or their physicians, but as their design team, before whom they are not children but products, results. Nevertheless, might we not be confident that if this pitfall is clearly understood, and if the defining intent of parents and physicians is not to control persons but to prevent their illness, it would be possible for persons to come into existence this way without their sense of self-in-relationship being compromised?

For people of religious conviction, intentions count very much in assessing the goodness of an act, and for that reason we are deeply suspicious of the integrity of our own intentions. And so we believe that it is possible to do these things with the right intent, but doubt that we will do so always or even frequently. How can we be confident that we will have such "careful, constrained efforts"? Would it ever be the case that the "defining intent" of all who participate in a specific use of this technology is healing, not control? How would we know this even for ourselves, much less for others? As a rational human being I find myself inclining to accept the suggestion that good intentions may jus-

tify this technology, but as a Christian theologian I am skeptical precisely because my theology teaches me not to trust the clarity and purity of my own moral reason and to entertain serious doubts about the moral integrity of others. I mention this because I believe it is urgent that people of other faiths or philosophies understand just how sober is the Christian assessment of human moral nature, and thus why there is a tendency toward skepticism about how technology will turn out, not because of technology's failure to perform as we intend, or even because we intend badly, but because our good intentions are at best confused and corruptible midstream. This has nothing to do with technical prowess or safety and everything to do with our universal lack of "purity of heart," what the Danish philosopher and theologian Søren Kierkegaard said is to will one thing.

This skepticism applies, of course, not just to the prospect of human germline modification but to all our human undertakings, and so obviously almost no one takes it as a basis for halting all forms of human action or technology. It points, minimally, to the need for candor about intentions and for clarity about them. Do we intend this technology for healing or for profit and enhancement? Will it increase compassion or injustice? And since Christian theology, at least, predicts that the answer is both, the practical question becomes: How can we structure the development, use, and deployment of this technology to favor compassion and not injustice? How do we prejudice its development toward the most urgent health needs and away from less urgent ones? How do we assure universal access to its most important benefits, and what policies will make it most just in the distribution of its benefits and risks? Theology is interested, not so much in a technique in isolation, but in its full context of funding, social factors, and public policy.

Aside from these matters of intent and context, some religious people have said that certain uses of biotechnology amount to "playing God" and must be opposed at all costs. Perhaps the most famous statement of this view is from Paul Ramsey, who said, "Men ought not to play God before they learn to be men, and after they have learned to be men they will not play God."[3] This warning about "playing God" has meaning for many, including those outside the faith traditions, and it is often found in the secular media to call attention to the serious stakes raised by human applications of genetics. It points to a limit on the proper scope and sphere of human action, suggesting perhaps that as creatures human beings ought not to expand our place in the cosmos and take up the role of creator. To push beyond the sphere of creatureliness or to refuse

to accept the strictures of our finitude is to refuse to be a creature and thereby to refuse the practical meaning of the existence of God. "Playing God" is therefore arrogant and ultimately a functional expression of atheism. It is not so much a violation of a special zone within the creation where God alone can know and act and determine the outcome of events, as if God alone knows our DNA, but a refusal on our part to stand back from that part of creation over which God alone has the right to determine what will be.

For some, matters of human genetics and especially human conception fall within God's determination and thus lie outside the scope of legitimate human action. For some in particular, the human embryo is inherently off limits as an object of experimentation. Those who make these arguments believe that our maturity as human beings lies precisely in our willingness to accept that we are limited, not in knowledge, power, and domain of action (which we can change), not by what we do not know or what we cannot do, but by what we are *prohibited* from knowing and doing. To be a creature is to accept finitude, to exist so far and no farther, to be blessed but also prohibited from seeking more than what we are given, and above all to be relieved of the responsibility of going farther and achieving all things imaginable.

On these assumptions, one might argue that human germ-line modification violates God's sovereign right to define the circumstances of every human life. The technology interposes itself between the creator God and the human creature, intruding itself in that mystery by which the creator begins to determine, define, and establish the unique identity of each person. Earlier, I developed the argument that a designed person cannot truly become a person in relation to those who collaborate in the design. Now we are considering a theological version of this argument, which is far stronger, if its assumptions are granted, than its anthropological correlate: germ-line modification would violate a moral limit on human action by depriving God of God's sovereign right to determine how human life is brought into existence. God alone is God; God alone is creator.

The violation, in fact, is twofold. First, it distorts the relationship between God and the life affected by the action. God alone is the maker of each life. To interfere is to violate the integrity of the God-creature relations by inserting a third party, another "god" who preempts the place of God. Second, it distorts the relationship between God and the one who acts, between God and the scientist or the physician. God authorizes human action within limits, and human actors—in this case, physicians and genetic engineers—must confine

their actions to those limits if they are to respect the relationship in which they stand before *their* creator. In the exuberance of creativity and in the sheer joy of helping another, we should never fail to remember that we are creatures, not creators.

Against such heavy-handed theologizing, many today will protest, and one of the first lines of protest is the charge that God doesn't always do a very good job as the creator of human life, and so it should be perfectly acceptable (if not obligatory) for us to help out. But for religious people who accept these assumptions, that counterargument is entirely beside the point. The issue is not whether God is doing a good job—not to mention a perfect job—at this business of causing genetically sound conceptions, but simply that it is God's job to do, and ours is to accept the fact that we are God's creatures. Consider this text from Hebrew scriptures, one that is widely familiar in Christian churches:

> Woe to you who strive with your Maker,
> earthen vessels with the potter!
> Does the clay say to the one who fashions it, "What are you making?"
> or "Your work has no handles"?
> Woe to anyone who says to a father, "What are you begetting?"
> Or to a woman, "With what are you in labor?"
> Thus says the Lord,
> the Holy one of Israel, and its Maker:
> Will you question me about my children,
> Or command me concerning the work of my hands?
> I made the earth,
> And created humankind upon it;
> It was my hands that stretched out the heavens,
> And I commanded all their host. (Isaiah 45:9–12)

It is a violation of our limited status as creatures to give advice to our creator, much less to take over any parts of the creator's work on the presumptuous view that we can do it better. This steals from the creator the right to be the creator and places that right in human hands, thereby hopelessly blurring the line between creature and creator, with catastrophic consequences for the creature.

But surely, we moderns argue, do we really think that if our technology makes people healthier than they otherwise might have been, that we have violated their relationship with their creator? And if it did, what makes us think

they would mind that, considering the alternative? Here again, modern protest misses the point. There is a God, the creator of all, whose right to define all creation is not to be compromised, second-guessed, or interfered with. This God has a relationship with every creature, and no other creature can interfere to redefine that relationship. From that relationship flows the value of each creature and the meaning of each life. Each creature comes from God and returns to God, the source and destiny of all.

I find this theological protest disturbing but not persuasive. It is based, I believe, on a theological view of human nature that is no longer tenable, precisely because of what theology should learn from the biological sciences and from the theory of evolution. It is simply not the case that human nature is fixed or unchangeable or that God has defined it once and for all time. Indeed, human nature at its core is characterized precisely by its open-endedness and by the invitation each person is given to define his or her own life and identity. This gift of open self-definition is described by the great mid-twentieth-century Catholic theologian, Karl Rahner, in the context of his consideration of the prospects offered by genetic self-modification. "Man, as the being who is free in relation to God, is in a most radical way empowered to do what he wills with himself, freely able to align himself towards his own ultimate goals."[4] Drawing on philosophical terms and especially on the resources of mid-twentieth-century religious existentialism, Rahner says, "When his essence is complete it is as he himself has freely created it."[5]

But what about human nature, either as evolved or as created without intermediary by God? Must we not respect the biological givenness of our humanity and refuse to manipulate it, out of fear that in so doing we will undercut the very foundation of our freedom? Rahner does not find this persuasive: "At this point the theologian who proceeds by means of ontological categories finds himself in severe difficulties, for there is little, indeed almost nothing, in man's biological constitution which he can recognise as necessary to his nature."[6] So here we have a theologian of the highest stature who seems to endorse the most sweeping applications of the technologies of human self-modification.

Rahner, however, counterbalances his own approval with profound concern, and on balance appears to reject any possibility of the use of genetics to modify the biological givenness of our humanity. Interestingly, the approval and the objection are developed in two different essays, almost as if we were dealing with two different theologians. More precisely, however, we are in fact

facing here two conflicting strands in Christian theology. On the one hand, theology recognizes that human beings are created to create, and that it is our failure to act in nature, rather than our action, that betrays our creaturely essence. In Rahner's case, this creativity is taken to the point of self-definition, the self-assertion of the creature as a subject before God but nevertheless as a subject, not as mere object. All this is embraced in the traditional notion of human beings as creatures in the image of God.

But, on the other hand, theological tradition recognizes that being in the image of God is only half the truth of our human nature, that we are also rebels against this relationship with God and against the freedom it entails. It is our created destiny of freedom that we reject, choosing instead a self-created and false freedom through the illusion of control over life and existence. Rahner warns: "What, in actual fact, is the driving force behind genetic manipulation? What sort of person is driven to it? And the answer would be, in the first place, the hate of one's destiny; and, second, it is the man who, at his innermost level, is in despair because he cannot dispose of existence."[7] Rejecting freedom and its risks, we turn instead to power and its predictability at the expense of freedom, our own and that of future generations. This objection is also stated by C. S. Lewis: "What we call man's power over Nature turns out to be a power exercised by some men over other men with Nature as its instrument. . . . All long-term exercises of power, especially in breeding, must mean the power of earlier generations over later ones."[8] The warning here from theology is that in grasping for freedom through power over nature, we will use nature to exert power at the expense of freedom.

These conflicting views from Christian theology—on the one hand, that we are created to create, and on the other, that power over nature (technology) is power over others—are both found in religious circles today and in the publications of scholars and communities on questions of genetics. On the one hand, we find the most profound affirmation of human creativity, as contributing to nothing less than the glorification of the creator through the expanding possibilities of the cosmos. Seen solely from this side of the conflict, we human beings should go forward with daring applications of our technology, even to the point of designing our own biological transcendence. On the other hand, we find the most worrisome expression of human destructiveness, not as something we intend but as something that is inevitably mixed in with our best work. In this view we cannot help but destroy, and so we are better off not helping at all. My own view is that this conflict is deeply grounded in our

theology and, perhaps for that reason, found almost everywhere that serious people are talking about the shape of the human technological future. Our future both tantalizes and frightens us, and it should.

NOTES

1. Lee M. Silver, *Remaking Eden: How Genetic Engineering and Cloning Will Transform the American Family* (New York: Avon Books, 1997, 1998), 291.
2. Ibid., 292–93.
3. Paul Ramsey, *Fabricated Man: The Ethics of Genetic Control* (New Haven, Conn.: Yale University Press, 1970), 138.
4. Karl Rahner, "The Problem of Genetic Manipulation," *Theological Investigations,* vol. IX, tr. G. Harrison (New York: Seabury, 1966), 205–22 at 212.
5. Ibid., 205–22 at 213.
6. Karl Rahner, "The Experiment with Man: Theological Observations on Man's Self-Manipulation," *Theological Investigations,* vol. IX, tr. G. Harrison (New York: Seabury, 1966), 225–52 at 232.
7. Ibid., 225–52 at 245.
8. C. S. Lewis, *The Abolition of Man* (New York: Macmillan, 1965), 69.

CHAPTER THIRTEEN

# Germ-Line Intervention and the Moral Tradition of the Catholic Church

Albert Moraczewski, O.P., Ph.D.

From the outset the reader should be clear about the perspective from which this chapter is written. It is an honest effort to state with accuracy and clarity what the moral tradition of the Catholic Church says on the matter of germ-line intervention. To be precise, it should be noted that only the head of the Church (the pope), general councils in union with the pope, and bishops united to the pope in their respective jurisdictions can speak authoritatively for the Church.[1] No individual bishop or Bishops' Conference, or a fortiori no priest or lay person, can speak, on their own account, for the Church. However, all the above can present and teach what they hold to be Church teaching by citing relevant official documents in support of their assertions. This chapter is just such an endeavor.

The principal authoritative documents used in this essay include the sacred Scriptures (as interpreted by the Magisterium[2] when there is doubt or conflict regarding the meaning of a biblical text), the documents of Vatican Council II, and the *Catechism of the Catholic Church* (hereafter *CCC*),[3] which was produced by a host of scholars drawing on a rich collection of previous Church documents, ancient and modern, reviewed by all the Catholic bishops and ap-

proved by Pope John Paul II on June 25, 1992. The pope subsequently ordered its publication on October 11, 1992, in an Apostolic Constitution in which he stated: "[It] is a statement of the Church's faith and of Catholic Doctrine. I declare it to be a sure norm for teaching this faith and thus a valid and legitimate instrument for ecclesial communion."[4]

It should be noted that with regard to the sacred scripture for Christians, the Bible is normative for the morality of human behavior. For Catholics, the Bible is normative, but with the proviso that the Church believes that Jesus has given her the power to articulate an authentic interpretation of its teachings.[5] This having been said, the challenge for the Church is to apply the relevant teachings to contemporary issues.

Clearly, one would not expect to find in the Bible an explicit treatment of modern biological developments. Hence, one must find pertinent biblical teachings that can reasonably be applied to the issue. It is not a question of "proof texts," of isolated statements, often taken out of context and forced to carry an inappropriate burden, but a matter of presenting a view that reflects the overall teachings of the Bible. Respect for human life, for example, which is a central value in both the Jewish and Christian faiths, is represented by the fifth commandment, "You shall not kill,"[6] and is a theme woven throughout the sacred scriptures, especially in the New Testament.

To understand the meanings of biblical statements, the Church today consults the early church fathers (bishops and theologians who wrote in the first six centuries of Christianity), formal teachings of the Church's ecumenical councils, such as that of Nicaea (325), Chalcedon (451), Vatican I (1870), and Vatican II (1965), and the writings of contemporary theologians, especially biblical exegetes.[7] The composition of the *CCC* itself is one example of such a process.

In its moral analysis of specific issues, such as the use of newer reproductive technologies, the Church depends on an accurate description of the biological and medical facts supplied by relevant experts in the field. The Church will then consult a variety of scholars and theologians who have sought to provide theological or ethical reflections on the issue under consideration. Then if it is judged that the matter requires a specific intervention by the Church, the appropriate dicastery (an agency of the papal curia), or the pope, will make a statement such as was done with regard to in vitro fertilization (IVF) by the Congregation for the Doctrine of the Faith (*Donum vitae,* 1987) and to treatment withholding/withdrawing (Declaration on Euthanasia, 1980), while Pope John Paul II explained in some detail the Church's

teaching on the sacredness and dignity of human life (John Paul II, *The Gospel of Life,* 1995).

And so it is with the matter of germ-line genetic intervention. While the Church has not yet published an official document on the specific issue, great caution must be employed in this matter because of the dignity of the human person and scientific uncertainties. Although Pope John Paul II welcomed genetic therapy with its great promise of benefit, he urged extreme caution in the manipulation of the human genome. Theologians are free to propose moral analyses based on the Church's moral tradition or to venture forth into new territory with other lines of argumentation, subject to the authoritative evaluation by the Church.[8]

As noted, in the moral tradition of the Catholic Church there is no direct treatment of the issue of genetic intervention on human germ-cell lines. It hardly need be said that the issue is too new for such to have occurred. Yet the Church has not been totally silent on the matter in recent times, for Vatican Council II and the popes since Pope Pius XII have made some significant statements on genetics-related topics. In addition, there are long-standing moral principles such as the inherent dignity of all human beings and the sacredness of human life that are part of that tradition and which can speak to the issue of germ-line genetic intervention.

But of more fundamental importance, the Church considers herself to be particularly competent to deal with certain prior issues that must be addressed before making a specific assessment of this genetic technology. Of concern here, then, is not simply the technology of genetic intervention on germ-line cells as such. Rather, it is the application of this technology to *human* germ cells (or very early embryo),[9] whether with therapeutic or enhancement intent. These germ-line cells, once "mated," will ultimately develop—barring external interference or internal developmental obstacles—into adult human beings.

The ultimate subjects of this technology are human beings, and not only isolated, individual human beings but an indefinite number of subsequent generations and the human communities to which they belong. Therefore, it is of primary importance to know what human beings are and what their purpose is. Only with this knowledge will we have a solid basis for judging the significance and impact of genetic intervention (or of any other technological intervention) on human germ-line cells.

This chapter will first present what the Catholic Church believes humans to be and what their purpose for existence is. Then in the light of the first part, this chap-

ter will consider what principles in the Church's moral tradition may be applicable to the issue of germ-line genetic interventions. Applying these principles to the proposed technology, the chapter will conclude with a qualified evaluation.

## The Human Person

The Declaration of Independence of the United States, albeit a secular document yet with quasi-religious foundations, states: "We hold these Truths to be self-evident, that all Men are created equal, that they are endowed by their Creator with certain unalienable Rights, that among these are, Life, Liberty, and the Pursuit of Happiness."[10] This document argues, as a common heritage of our nation, that all men, now understood to mean all members of our society, that is, all men and women regardless of their social, economic, or racial status, are created by the Creator and possess those "unalienable rights." One exception, however, is made by the current interpretation of the civil law, which allows the unborn child to be deprived of all three "unalienable Rights," it would seem, almost at the whim of the mother.

The moral tradition of the Catholic Church does not depart from this value statement of the Declaration, but goes beyond it.[11] The Psalmist, in the Hebrew scriptures, full of wonder, rhetorically asks in Psalm 8:5–7:

> What is man that you should be mindful of him,
> or the son of man that you should care for him?
> You have made him a little less than the angels,
> and crowned him with glory and honor.
> You have given him rule over the works of your hand,
> putting all things under his feet.[12]

These words should be read against the background of the opening chapters of the book of Genesis, particularly Genesis 1:26–31:

> God created man in his image;
> in the divine image he created him;
> male and female he created them.

God blessed them, saying: "Be fertile and multiply; fill the earth and subdue it."

In chapter 2 of Genesis (vv. 18–20), the second account of creation, Adam is given the power to name all creatures. It should be recalled that among many

primitive peoples the ability to name something (or, sometimes just to know the name), be it living or inanimate (e.g., a piece of land to be claimed for one's country), is to have some power over that entity. In today's world there is an analogous situation with chemical names. A competent chemist with a knowledge of a compound's full chemical name (its structure) can synthesize that compound and surmise some of its properties. Similarly, in biology knowledge of an organism's genome provides a clue to its nature. In both cases we have some degree of control over those beings.

These foundational biblical statements are the starting points for the Church's reflections regarding the nature and meaning of man. So, then, what is the human person? And what is the purpose of his existence?

1. He is a creature, that is, a being freely made by, and dependent on, the Creator (see *CCC* #295–96, 355).
2. He is fashioned in the image of the Creator (see *CCC* #702–6), who is not simply a force, an "it," but a personal being who knows and loves (see *CCC* #203–7). Furthermore, this Creator, who is also called "God" and "Lord," is not part of the universe; nor does this Creator depend on it in any way (see *CCC* #205).
3. Because the human person was created with an intelligence by which he can know truth and a free will by which he can choose (or reject) the good, unlike other living forms, he is morally responsible and accountable to God.
4. In spite of the human person having originally rebelled against God (see Genesis 3:1–19), and continuing to do so by his sins, all human beings are invited by God to an eternal life which involves an intimate and unbreakable blissful union of one's total being with God (see *CCC* #210, 27, 30). The concept of "invitation" includes the notion that the individual can accept or decline that invitation. And indeed that acceptance or refusal is expressed by the quality of one's moral life. One might say that this goal—union with God—is the ultimate extension of the "pursuit of happiness" stated in the Declaration of Independence.
5. In a way, the human person is an enigma, a mystery, a being who partakes of material nature and yet transcends it. Although he may, in his temporal present state, experience internal tension, in part due to this makeup of matter and spirit, and in part due to his fallen human nature, he is, nonetheless, truly one being[13] (see *CCC* #362–68).

In brief, the Catholic Church defines the human person, body and spirit, as created in the image of God and invited to be united to God as his ultimate reason for existence, in an eternity of bliss (see *CCC* #1023–29). But to describe the purpose (or, meaning) of the human person more fully, we need to look also at his *proximate* purpose.

## The Human Person's Proximate Purpose

The meaning and purpose of the human person is found not only in his ultimate purpose—eternal union with God—but also in his temporal and proximate purpose as the Catholic Church understands it to be. In the first creation scene in the Bible, God instructs Adam and Eve (representing the human race): "Be fertile and multiply; fill the earth and subdue it" (Genesis 1:28). Contemporary writers interpret this command as inviting humans to be "co-creators"; to use responsibly the resources of this world and to shape it to be a more friendly environment for human occupation.

Clearly when the concept of creation is used in relationship to God, reference is made to God's bringing into existence the entire universe and its components from absolute nothingness (*creatio ex nihilo*) (see Genesis, chapter 1; 2 Maccabees 7:28). But, when applied to humans, "co-creative" does not refer to the *ex nihilo* act of God but rather to human participation, as a secondary cause, in the transformation or shaping of material things for some intended human goal and need, such as making objects of usefulness, or of beauty, or for amusement (see *CCC* #306–8).

A special case of co-creativity is human reproduction. Indeed, in human reproduction (better termed "procreation") human beings are brought into the world by a collaborative effort, as it were, of God and the human couple (except today, a woman could clone herself).[14] God creates *ex nihilo* the human soul while the couple through the instrumentality of their respective gametes, oocyte and spermatozoon, produce the body. But note again that no dualism is necessarily implied here (a persistent but unnecessary philosophical problem since Descartes). After fertilization, the zygote, which results from the "fusion" of the male and female pronuclei, and just prior to its cleavage into two daughter cells receives a human soul by a creative act of God. The human soul is a principle, not a distinct thing, the principle of human life, unity, and specificity. This occurs when the physical body (the zygote at this stage of development), the material principle, is suitable for animation by a spiritual principle,

the human soul. These two *principles,* material and spiritual, constitute one existing physical being (thing), the living human person (see *CCC* #362–67). This new living human organism (the zygote and subsequent embryonic and fetal stages) in the eyes of the Church is to be respected and treated as a human person,[15] even in his most elementary physical state. From the moment of conception (i.e., completion of fertilization)[16] it is an *actual* human being, but will be sequentially (apart from accident or disease) a born human child, a human adolescent, a human adult. As this new human organism, just conceived, proceeds successively through the various developmental stages, its human potentialities are gradually actualized, all the while being an actual human person, a subject of the basic moral rights from the beginning of its existence.[17]

## Relevant Moral Principles

The book of Genesis (1:26–28) and the Catholic Church (*CCC* #373) teach that the human race received the mandate to develop the earth and its many resources to meet its practical needs (e.g., food, clothing, shelter, etc.) and to contemplate and praise God as He is reflected in His creation. The point of departure for a consideration of the relevant moral principles is the Church's recognition that God attached a limit and an accountability to the delegated dominion (i.e., stewardship) given to humans over nature when he issued that mandate: "You are free to eat from any of the trees in the Garden except the tree of knowledge of good and bad. From that tree you shall not eat" (Genesis 2:16–17a). There was not only a limit imposed but also a consequence for violating that limit: "the moment you eat from it you are surely doomed to die" (Genesis 2:17b).

But difficult to determine are the specific limits we are to observe. Some major parameters in the Hebrew Bible are found in the Ten Commandments (see Exodus 20:2–17), for example, "You shall not kill. . . . You shall not commit adultery. . . . You shall not steal." From the Christian Bible is the universal command, "Love your neighbor as yourself" (Matthew 19:19b), of which the Ten Commandments are particular expressions. In the parable of the Good Samaritan (see Luke 10:29–37), Jesus explains that "neighbor" means all humans, but especially those in need.

These Commandments presume that humans are able to discern the truth and able to love the good. Implicit is that humans are freely able to choose among options (see *CCC* #311, 1704–5). Although humans radically possess

freedom of choice, free will, this does not eliminate the fact that there is a variety of forces or influences, internal and external, which can limit, to varying degrees, our freedom to choose. The radical ability to know universal truths and freely to love the good is essential to what it means to be a human being.

Fundamental to an understanding of the Church's position on moral issues is the Church's insistence on the inherent dignity of a human person at any and all stages of development (see *CCC* #1934–35, 1700–1706). The source of that dignity is threefold:

1. Humans are created in the image of God (Genesis 1:27).
2. According to Christian belief, humans are redeemed by Jesus Christ (see Romans 5:15–19).
3. Humans are called to eternal friendship with God, the Creator of all that is (see Romans 8:18–34).

This dignity is inherent, that is, it is part of standard human equipment of each and every human being, without exception. It is not conferred by society nor by any institution but comes with human nature as an essential characteristic. It applies to all stages of human development from conception (the formation of the zygote) until natural death. From this perspective, even the earliest human being (the zygote) is the subject of basic human rights, especially the right to life.[18] The intentional and deliberate termination of an innocent human life, even at the zygotic stage, is considered by the Church as a grave moral evil, a serious injustice.

One clear limit to what we may do to a human being—at whatever stage of development—from the Church's perspective is that we may not induce changes in a human person or persons that would eliminate or impede the two capacities of knowing and loving. Even though one may induce a temporary state of unawareness such as by sleep or by general anesthesia when there is a proportionate reason that pertains to the well-being of the individual, such as general anesthesia in connection with surgery to induce muscle relaxation and unawareness of pain, one may not do so on a permanent basis.

## Application of Moral Principles to Germ-Line Genetic Intervention

With regard to genetic intervention, whether somatic cell or germ-line intervention, including the very early embryo, Catholic moral tradition not only

prohibits killing the zygote, the embryo, the fetus, and the born child, but also prohibits any procedure that is directed to altering the basic human nature of these beings.[19] The above having been said, there is another significant and relevant question which is the focus of these reflections: Do the Catholic moral tradition and teaching prohibit absolutely any genetic manipulation, whether on somatic cell or germ-line cell? Would such genetic manipulation exceed the limits of the delegated dominion (stewardship) granted to humans by God?

Since our knowledge of genetics and its relationship to our bodily structure and function is relatively recent, and our ability—albeit rather limited—directly to control and modify our genome is even more recent, there is no Catholic tradition on that specific topic. And, of course, there is no explicit biblical teaching on the matter of genetic manipulation; but there are nonetheless some biblical and Church teachings that have a bearing on the topic, as we have seen in the above reflections.

The current pope, John Paul II, has made several supportive remarks about genetic manipulations although he has not made any extensive statements about the subject. For example, to a study group on biological research sponsored by the Pontifical Academy of Sciences the pope noted the following: "The research of modern biology gives hope that the transfer and mutations [i.e., the deliberate alteration] of genes can ameliorate the condition of those who are affected by chromosomic diseases [i.e., genetic diseases]; in this way the smallest and weakest of human beings can be cured during their intrauterine life or in the period immediately after birth."[20] In addition, he noted the distinction between therapeutic and enhancement genetic procedures.[21] He was not opposed to the former so long as the basic moral rights of the person were not violated. However, with genetic manipulation directed to enhancement, the pope saw some very grave moral problems. Yet he did not place an absolute ban on such genetic activity but cautioned that very important reasons would be required to justify such an endeavor even if done on a limited scale with appropriate safeguards.

As a general operative principle, in his very first encyclical of his pontificate, John Paul II reminded the Church, and indeed all members of the human race, that there are limits to technology's reach: "The essential meaning of this 'kingship' and 'dominion' of man over the visible world, which the Creator himself gave man for his task, consists in the priority of ethics over technology, in the primacy of the person over things, and in the superiority of the spirit over matter."[22]

It is well to note that the Catholic Church does not have a radical bias against

technology. The Church explicitly teaches that it does not consider these technological endeavors to be in competition with God. Rather, they are a further manifestation of God's Glory: "But the progress of science and the inventions of technology show above all the infinite greatness of God, Who created the universe and man himself."[23] "Far from considering the conquests of man's genius and courage as opposed to God's power as if he set himself up as a rival to the Creator, Christians ought to be convinced that the achievements of the human race are a sign of God's greatness and the fulfilment of his mysterious design."[24]

These several statements were made before genetic intervention became a practical reality. Notwithstanding that chronology, I believe that the Church's teaching on this matter has not changed. As long as the genetic change (of the somatic cell variety) intended, or actually occurring, is therapeutic for the individual who is the subject of the genetic manipulations, and the appropriate informed consent has been obtained, there would be no significant moral objection. Of course, this is also presupposing that the individual is not deliberately subjected to a basic change in his human nature, such as losing the ability to know the truth and freely choose the good. Of course, in the case of germ-line genetic intervention the moral analysis is more complicated because not-yet-existing individuals are involved.

The above having been said, another important consideration must be reviewed: what about the means, the procedure, employed to carry out the proposed germ-line genetic alterations? The Church has some serious points to make about human procreation and the status of the zygote and the very early human embryo and the act of procreation itself, particularly in two documents, *Humanae vitae* and *Donum vitae*.[25] Both documents stress human dignity, applicable to all persons, at all stages of development, and are concerned with protecting the life of the newly conceived human being as well as underlining the sacredness of the act of human procreation (the conjugal act). By sacredness is meant that the act of human procreation is distinct from animal reproduction—even if it shares some of the same biological elements. Human procreation is distinct because it constitutes an activity that engages the man and woman on several levels of their reality—biological, psychological, social, and spiritual—and is inherently directed to the coming into being of another human person. Furthermore, that living human being which can result from the "conjugal act" is destined to a life that transcends this world, an eternal life that is a true sharing in the divine nature itself.

According to current technology, any germ-line genetic manipulation would

require that the gametes (or the very early embryo) be isolated in vitro in order to insert a corrective gene or perform some other alteration of the genome. Then if the "making" of a human being with the altered genome were the desired objective, in vitro fertilization (IVF) followed by embryo transfer and implantation (ET) would be the ordinary way to accomplish this purpose. But the Church has already expressed its disapproval of IVF in its 1987 statement, *Donum vitae,*[26] because the Church views IVF as opposed to human dignity and the sacredness of human procreation.

## Conclusion

The first part of this chapter was devoted to establishing that the Catholic Church holds human beings to have been created by God, along with the remainder of the universe, but in a special category. While sharing with other forms of life on earth many aspects of a material living being, such as the DNA structure and its code and the need for some sort of food and energy source, the human person transcends all other life forms, including the higher primates such as the chimpanzee and gorilla, by virtue of the fact that humans possess a spiritual soul, a nonmaterial principle of life. Biblically stated, humans are made in the "image of God" (Genesis 1:27). In the biblical creation accounts, this is not said of any other life forms.

The ultimate purpose for humanity's existence on earth, according to the teaching of the Church, is eternal, blissful union with God.[27] The proximate purpose of human existence is to subdue the earth, not in a destructive manner but by utilizing the world's resources and human skills to fashion the environment into a suitable place for human habitation—in its "pursuit of happiness"—and a locus for the worship of God.

Rooted in the Church's understanding that humans, all humans, are made in the image of God, the Church expresses in her teaching that there is an inherent dignity possessed by each and every human being regardless of the stage of development, race, socioeconomic status, religion, nationality, age, or health. Associated with that dignity is the recognition that the life of each is sacred and that it is a serious moral evil to deprive deliberately and unjustly human beings of their life or of their physical and mental integrity. Not always perceived clearly, the Church also holds that the origin of individual human life, that is, the procreative act between a husband and wife, is a sacred act, and is to be respected as such.

Applying the above principles and understanding to the issue of germ-line genetic intervention, it was concluded, by extrapolation, that such intervention on human germ-line cells if done with a clear therapeutic intent could be morally acceptable provided that the process met certain conditions: *if* the process did not destroy or impede essential components and processes of human nature, such as the capacities to know and love humanly, and *if* other issues such as safety, efficacy, and free, informed consent of future generations could be resolved. Another major caveat is that the means employed to insert the gene into the gamete and subsequent fertilization should not involve IVF or other procedures that the Church deems to be contrary to the dignity of the resulting human being and the sacredness of human procreation.

While the Catholic Church may be perceived as being conservative, especially with regard to technological developments, this does not reflect an opposition to technology. The Church just wants to make sure that these are truly for the well-being of human persons and are applied justly and equitably for the authentic flourishing of the human race.

NOTES

1. See Vatican Council II, *Dogmatic Constitution on the Church* [*Lumen Gentium*], #8, #18, and *Code of Canon Law* [1983], #331–34.

2. The official teaching authority of the Catholic Church for which the pope is the primary spokesperson and those to whom such activity may be delegated (e.g., the Congregation for the Doctrine of the Faith).

3. *Catechism of the Catholic Church (CCC),* English translation (Liguori, Mo.: Liguori Publications, 1994).

4. John Paul II, *Fidei Depositum,* The Vatican, October 11, 1992, #3.

5. See *CCC* #119.

6. Exodus 20:13; see also *CCC,* Part Three, Article 5.

7. See *CCC* #110–19.

8. See "The Ethics of Genetic Manipulation," an address of Pope John Paul II to members of the World Medical Association, October 29, 1983. The text was reproduced in *Origins* 13 (November 17, 1983): 386–89.

9. While some authors would use the term *pre-embryo* to describe the stage of embryological development between the zygote and implantation, it is not a biologically valid term. Princeton biology professor Lee M. Silver observes in his recent book: "I'll let you in on a secret. The term pre-embryo has been embraced wholeheartedly by IVF practitioners for reasons that are political, not scientific" (*Remaking Eden: Cloning and Beyond in a Brave New World* [New York: Avon Books, 1997], 39).

10. *The Random House Dictionary of the English Language,* unabridged edition (New York: Random House, 1966), 1936.

11. See, for example, *CCC* #1934–35.

12. All biblical references are from *The New American Bible* (Washington, D.C.: Confraternity of Christian Doctrine, 1970).

13. Although composed of body and soul, these are not two distinct things but two principles, each incomplete in itself. Together they constitute one complete thing, one being, the existing, living person.

14. She could do so by using the nucleus from one of her somatic cells and fusing it with one of her oocytes which had been enucleated. Thus, she would have provided the entire genome for the new organism. Of course, there are serious moral objections to that procedure.

15. The cautious wording reflects the fact that, up to this point, the Church has not officially and specifically stated that ensoulment, that is, the infusion by God of a spiritual soul, takes place at the very beginning when the new human organism is constituted. (See Congregation for the Doctrine of the Faith, *Declaration on Procured Abortion,* November 18, 1974, footnote 19.)

16. There are some writers today who, contrary to previous scientific and medical understanding, would hold that conception begins with implantation.

17. See Benedict Ashley and Albert Moraczewski, "Is the Biological Subject of Human Rights Present from Conception?" in *The Fetal Tissue Issue,* ed. Peter Cataldo and Albert Moraczewski (Braintree, Mass.: The Pope John Center, 1994), 33–59.

18. Ibid.

19. See Congregation for the Doctrine of the Faith, *Donum vitae* (Instruction in Respect for Human Life in Its Origin and on the Dignity of Life), Vatican City, 1987, I, esp. #1 and 4; also *CCC* #2256–62, 2270–71, 2274–75. The document is reproduced in Kevin D. O'Rourke and Philip Boyle, eds., *Medical Ethics: Sources of Catholic Teaching,* 2nd ed. (Washington, D.C.: Georgetown University Press, 1993).

20. Pope John Paul II, English translation in *Origins* (November 4, 1982): 342.

21. "In particular, this kind of intervention ["aimed at improving the human biological condition"] . . . must . . . respect the fundamental dignity of mankind and the common biological nature which lies at the basis of liberty . . . and [avoid] . . . manipulations tending to modify the genetic store and to create groups of different people, at the risk of provoking fresh marginalizations in society" (John Paul II, "The Ethics of Genetic Manipulation," an address to the World Medical Association, October 29, 1983, English translation, *Origins* 13, no. 23 [November 17, 1983]).

22. Pope John Paul II, *Redemptor Hominis,* March 4, 1979, no. 16.

23. Pope John XXIII, *Pacem in Terris,* April 11, 1963, no. 3, English translation by the National Catholic Welfare Conference.

24. Encyclical of Pope Paul VI (*Humanae vitae*) and Vatican Council II, *Gaudium et Spes,* December 7, 1965, no. 34.

25. Congregation for the Doctrine of the Faith (*Donum vitae*).

26. See above note 19.

27. *CCC* #27: "The desire for God is written in the human heart, because man is created by God and for God. . . . The dignity of man rests above all on the fact that he is called to communion with God" (Vatican Council II, *Gaudium et Spes* 19.1); see also *CCC* #1703.

CHAPTER FOURTEEN

# Uncountable as the Stars

## Inheritable Genetic Intervention and the Human Future—A Jewish Perspective

Laurie Zoloth, Ph.D.

> In blessing, I will bless thee, and in multiplying I will multiply thy seed as the stars in the heaven, unknowable. GENESIS 22:17

The first promise of the covenantal relation that forms the basis of Judaism is the one of a predictable fecundity. Abraham is promised children, not empires or kingship. However, while the people of Israel are promised uncountable generativity, it has been an assumption of the texts that the future generations would be unknowable—but linked together by the Law, backward to that moment of covenant, present with us at Sinai, and forward to an imagined future—hence the ongoing need for the study and practice of the commanded law, which creates a central way to shape the character of the children entrusted, *l'dor v'dor,* from generation to generation. But in our time, "generation" assumes ironic meaning as we turn our attention to new ways of making children that question the moral enactment of family, culture, and religion. Since the discovery of techniques to alter the human genetic code, scientists, ethicists, and legal scholars have sought to address the ethical issues created alongside the new organisms that molecular biological research has generated, in both federal regulations and standing commissions.[1] In the crafting of normative guidelines and in the search for the framing language to define the scope, nature, meaning, and goals of the research, society has sought justification and

argumentation to understand the enormous challenge such a discovery represents. At stake in this is a central Hellenistic idea that the narrative of the natural world is both sacred and inviolable, and that in tricking about with its alteration, we risk erring in the most ancient and classic ways—by unlocking secret knowledge and sending danger into the world. It is a theme that underlies many theological and philosophical traditions, the fear that knowledge is hubris, threatening the very order of the world.

In the contemporary period, the realm of genetic knowledge occupies the threatening theological location that cosmology or astronomy held in the medieval context, for it is in genetic knowledge that our ontological location and theological norms seem to be at risk.

For religious communities, the issues involved in the manipulation of human DNA are particularly challenging, opening historic tensions between the call to healing and the respect for human limits on generativity and procreativity. Many religions understand humans as limited not only by their ability to see and comprehend fully, but by the human creaturely condition, driven by hungers, temptation, passion, and the fear of death.[2] Linked to our concern that our enthusiasm for the science might blind us to its effects is the worry that our temptation for power or dominance might similarly confound our ability to control the use of this technology.

But is this idea of "nature" and of "danger" a vivid concern in Jewish texts? After all, Eve (*Chava*) is life, she is not Pandora. Chava looses resistance but also mortality, morality, judgment, discernment, work, and the facticity of childbirth. She does not release demons or lies.

For textually located religious traditions, such as Judaism, the turn to the canonical text can be difficult, since by definition, these are revolutionary technologies, and textual-based traditions operate within a framing system of logical and progressive casuistry. Hence, the search begins in these textually located, legally structured religious traditions for precedential religiolegal cases with similar moral appeals.[3] At stake are questions of principle, meaning, telos, and context, and these were precisely the questions raised in the AAAS project. Among religious traditions there is a widely shared presumption in favor of healing. Yet many religious traditions represented in the project also shared a deep caution regarding actions that might alter fundamentally and unalterably the human relationship to the given world. Such cautionary celebration has marked nearly every medical advance, and inheritable genetic modification (IGM) is no exception.

For the Jewish ethical-legal tradition (*halachah*), which functions methodologically as a discursive community in which the justification is created by the force of moral suasion, no single authoritative voice nor one particular council of authority speaks for the entire tradition or the community. Judaism itself is divided into four distinctive movements, each with a varying degree of allegiance to rabbinic and textual authority.[4] Hence, in confronting emerging ethical issues, what will serve best in the beginning to frame a coherent Jewish understanding of these issues is the widest possible call for inquiry and the widest possible response. In the *halachic* method, it will be the framing of the question that will determine the critical reflection that will emerge. Jewish ethics also is concerned with narrative ethics, or *aggadah,* justifying an approach with derived ethical norms suggested by extralegal sources (narrative, literature, history).

This chapter is a preliminary contribution in that direction in which I raise some framing questions for further debate and suggest some textual recourses. Like genetics itself, *halachah* tends to specific cases and to disaggregate the problem's aspects and components to better analyze them. Precisely because this critical issue raises problems far beyond those intended by the rabbinic codes of the law (*halachah*) that usually direct Jewish communal practice, I argue that what is called for in the Jewish community is a careful and creative discourse about how the range of Jewish thought might address such a challenge to the polity at large. This is a broader step than a strictly *halachic* review, since I want to raise a wider set of questions and draw from a wider set of texts and praxis, in addition to the centrally important *halachic* ones, and since it is intended to address the problem of how Jewish texts can be used by a broader social discourse. At stake in the *halachic* method of reasoning is the finding of cases which, while not having all of the same features as the case before us, have distinguishing moral appeals that might be similar to our case. For Jewish scholars, the question arises about how the contributions of Judaism can respond to ethical issues in the civic discourse, allowing for a distinctive insight. How can we struggle with the first responses of *halachic* texts to asking shared questions about issues of commodification, the nature of the self, the nature of "the natural," the limits of parental desire, and the justice obligation toward unconsenting future generations?

Let me state a framing claim: Jewish ethics is nonpathetic, based in duty, and in bioethics centrally, the duty to heal the sick. Duty organizes the entire system. The stance of the Jewish self toward the body, toward the earth, toward

the other is based on the duty to guard that which is not fully possessed, to be a *shomer* to all that is entrusted to us. Jewish ethics is attentive to both theological and secular issues. And let me state a framing moral geography: in the Jewish linguistic moral imagination, we are not in Gan Eden—a perfect world—we are in New York, in Vilna, in Babylon. Jewish ethics is attentive to secular concern. Secular issues are of concern to Jewish discourse for obvious reasons. The first is because secular anxieties create a specific social context to which religious communities respond. Cultural zeitgeist, cultural practices, and aesthetic sensibilities create the landscape on which the locus of Jewish discourse is situated. New medical theory creates the horizon of possibility and its terrors. Actual questions arise in practice, which are then translated into formalized *poskinim* (written questions) and answered with formalized written answers (*responsa*). Thinking broadly about the multiple dimensions of IGM will allow us to capture and creatively debate which features will allow us to create normative outlines for social policy. In this, *halachic* reasoning is a form of linguistic, definitional analysis, in which the parties to the debate seek epistemological commonality and define our significant differences as a first step.

## Are There Reasons in *Principle* Why Performing Inheritable Genetic Modification Should Be Impermissible?

Principled issues include assessments of the goal and meaning of the scientific inquiry; the ontological nature of the person; the intention and scope of medical intervention; the question of what constitutes disease and normality; the relationship between God and human partners; the tension between faith and science; and the problem of *l'dor v'dor* ("from generation to generation," referring to the transmittal of tradition, or to obligations between generations). Modern concerns shape the context for the contemporary use of classic sources in the current deliberation. However, the rabbinic discourse on medicine raises substantively different concerns, and hence, particular responses, than secular ones. Since germ-line research has not been the focus of medical questions that have arisen for actual patients, and since Jewish law is case-driven (no cases, no *responsa*), the literature is as yet thin, based on largely theoretical issues. Hence we can only debate fully whether the basic research should itself proceed or be halted. The intent of this work is to direct specific attention to this emerging issue and to stimulate serious inquiry in this direction.

As with all questions in classic Jewish argument, what is at stake here is not

whether there are essential principles that would prohibit an action, but how principles apply in specific cases.[5] Since Jewish ethical reasoning privileges the responsibility to save life above all other responsibilities, actions that save lives, hence nearly the entire medical arena, are the necessary focus of this account.[6] To turn away from possible healing activities is to neglect an important duty.

### *The Prominence of Life-Saving or -Extending Medical Intervention*

The first responses to germ-line intervention seem to indicate a general sanguinity with the procedure when it is framed as breakthrough medical therapy for life-threatening conditions. This entire category of response stems largely (although not entirely) from the defining moment in the Talmud in which the rabbinic authorities debate whether one can violate the mandate to rest and sanctify the Sabbath to rescue a man trapped in the rubble of a collapsed building. From this vivid (and, I might add, graphically obvious) source text springs a whole set of cases that are then defined as like being trapped—by illness, catastrophe, hunger, war, or threat. This has provided the warrant text for virtually all experimental therapy, including genetic research. (Limiting factors include the calculus of risk—if the therapy itself is more likely to threaten the life than to save it, as in the first organ transplants, then the risk/benefit ratio of healing is altered, and hence the intervention not permitted.) Hence, even if otherwise proscribed actions are involved (taking the organs of the dead, for example), the use is permitted if a specific life can be reliably saved. Such actions are not only permitted, *devar reshut,* but also mandated, *devar mitzvah.*[7]

### *The Nature of the Creative Act and the Nature of Human Creativity*

Can such an act of healing ever go "too far"? Is genetic engineering, in principle, a part of "world repair," *tikkun olam,* or an overreaching of human power? There are two important texts that recall a broad general concern for all of technology. The first is the creation of the Golem, a humanoid creature, by the manipulation of text and spells. This theme recurs frequently in the tradition: "Rava said: If the righteous wished, they could create a world, for it is written: 'Your inequities have been a barrier between you and your God.' For Rava created a man and sent him to R. Zeira. The Rabbi spoke to him but he did not answer. Then he said: 'You are from the pietists: Return to dust.'"[8] What is occurring in this text? Rava demonstrates that creation of some type of human life is possible: the man moves and walks, but does not talk. The work is flawed because of some inequity that must exist in Rava, the creator. The creation is

undone, sent back to dust. In later medieval rabbinic commentary on the text, the French interpreter Rashi notes that this sort of magical enterprise (in a way, the basic science of the time) was achievable by the manipulation of the letters of the name of God, the building blocks, as it were, of the Creator as known by humans.[9] The commerce is language: the word, the letters. In fact, in later Golem tales (the legend persists), the Golem has the Hebrew letters of the word *truth, emet,* carved on his forehead. By removing the aleph, the first letter in one of God's names, the Hebrew word for death, *met,* is formed instead, and the Golem vanishes. Further legends link the Golem not only with the chimera of "truth," but play with the Golem: all body, no spirit. The Golem in later tales is a revenging and powerful force: unlike the caricatured and vilified Jewish body, small, stooped, and awkward, the Golem of Prague legend is tall, muscular, and powerful, wreaking havoc on the Gentile enemy.[10] The Golem of Prague emerges to protect the Jews from the wrath of the Gentiles on the eve of Passover 1580, when the blood libel charges historically increased and led to pogroms. Yet as appealing as this image is to a persecuted people, we are warned of the essential error in the pursuit of this particular type of creationist research: the manipulation of the whole by its pieces does not lead to "truth," but to the excesses of spiritless power, unguided by faith, and ultimately dangerous. The texts are cautionary, but apparently not absolutely prohibitive; otherwise the story would not be so persistent.[11] The problem of the creation is *not* his creation, it is his existence as a being outside the subjugation of the Law.

The second cautionary text is the midrash on the construction of the Tower of Babel. Here the rabbis struggle with the problem of why the construction of a joint human project is seen as problematic, even when the ostensible reason for the construction is to "reach up to God." Finding nothing in the direct text, they describe a theoretical scene: "When a worker was killed, no one wept, but when a brick fell, all wept." What is occurring in this text? The rabbinic caution was that the use of humans instrumentally in a technologically impressive human project led to a dismantling of the distinction between persons and things. It took a long time to make a brick, hence, the brick became more precious than the human self. This decentering of human to thing was the catastrophe that felled the enterprise. The biblical text is in a pivotal textual location, after the Flood, prior to Sinai. The earth is not destroyed, nature restored, but humankind will need an Abraham, a covenant, and will begin the journey to the Law.

Is the wielding of such power an overwhelming reliance on science, a form

of *avodah zorah,* or idol worship? Is our love of science a decentering of God or Torah? Some could make the argument that replacing the centrality of God with an overwhelming attention to the human could create a false worship of science, or worse, of the perfected self. This is not a classic textual concern, and moreover this certainly does not distinguish IGM from any other sort of compelling science aimed at human alteration. In reflection on this problem, Joseph Soleveitchik, perhaps the central philosopher and *halachic* authority in contemporary orthodoxy, noted, "*Halachic* man is a man who longs to create, to bring into being something, new, something original. . . . This notion of *hiddush* (creative interpretation) is not limited to the theoretical domain, but extends as well into the practical domain, into the real world. The most fervent desire of *halachic* man is to behold the replenishment of the deficiency in creation."[12]

The act of genetic alteration may be bold and it may be inordinately dangerous, but it is not hubris; in fact, it is not a deflection from, but a recognition of, the human task to act in precisely this way, a boldness that is no different from other, rather spectacular interventions in the ordinary providence of human persons. "The dream of creation is the central idea in the *halachic* consciousness—the idea of the importance of man as a partner of the Almighty in the act of creation, man as creator of worlds."[13]

However, at stake in this science are questions about whether the deliberate manipulation of human DNA is taking God's primary creative role. In Jewish theology, the case for the dangers of usurpation of this role is weak (not absent, but weak) and the case for active imitation of God's role is made strongly. Humans are mandated to use and control the natural world actively, to act as partners in God's creation, and to do *tikkun olam,* to repair the world. The advertency or inadvertency of this act poses no unique problem, since by definition, creation is incomplete and is in fact unfolding in a world that is as yet unredeemed. Action by human persons is required to complete history. In fact, a *halachic* category exists to define compelling human or communal need, a *zoreckh* that defines such activity.[14]

### *Is Germ-Line Intervention Similar to Other Forms of Genetic Alteration or to Prohibited Mixing of Species?*

Biblical texts certainly warrant animal breeding, looking approvingly on Jacob's cleverness at animal husbandry. In fact, this example is cited by numerous commentators to support genetic manipulation. Other ways to alter the ge-

netic heritage of a particular family are to be supported and are mentioned in the Talmud. These include choosing a mate by clear selection of beauty or family heritage; avoidance of physical or mental "weakness" or disability; and exposure of married women who are leaving the *mikveh* (the ritual bath that is taken after menses and before the beginning of the period of the month in which sexual intercourse, and probably conception, is permitted) to the sight of a beautiful and learned man so that the children subsequently conceived will be learned. (Rabbinic folk medicine is based on premodern understandings of science and what we would now regard as a sympathetic magic.) If the selection of traits, the social construction of marriage, and external forces are used to influence our genetic shaping of the next generation, is the direct manipulation of the DNA a similar case?[15]

### *Can We Use the DNA Splicing Technique?*

The mixing of kinds in animal breeding and the grafting of unlike plants are forbidden in Jewish law. Is genetic engineering a kind of *kil'ayim,* or cross-breeding?[16] Responses to this question have focused on the issue in animals, where the prohibitions concern interspecies genetic transfer. Alteration within species, or enhancement of certain characteristics within species, has been accepted if the use is medical,[17] as in the use of pig heart valves for humans or the use of genetically engineered Factor VII for hemophilia, or insulin.[18] Others have noted that the grafting in genetic engineering is akin to the "grafting" that occurs during organ transplant, and thus is equally permitted.[19]

Immanuel Jakobowitz suggests a general response in his reflections on the problems of human cloning. Jakobowitz recalls that human holiness for Jews rests on cessation and not merely creation. Here he argues that *Shabbat,* not only for humans, but for God, represents this limit on production, creativity, and alteration of the world. Except for action needed to save lives in an immediate sense, even good human work, and even work in nature, is suspended in recognition of God's sovereignty.[20] Cognate cases include the theological limits on the boundaries of the *mishkan,* or tabernacle, the restrictions of *kashrut,* or kosher norms, and the general idea in Jewish thought that appetite, desire, business, and acquisition are to be limited and constrained by the social realities of a particular situation. The tension between unlimited freedom and social imperatives is discussed repeatedly in rabbinic debate. Finally, some argue that since DNA is not visible, it might technically fall under the rubric of arguments that permit things that cannot be seen to be unimportant. These are

technical standards that offer a footnote to the central theological arguments. It is the central premise of the Law itself. Shabbat is one of the first Commandments heard at Sinai—know the Law and live only by its limits. However, on Shabbat, even if thirty-nine great categories of work are stopped, both healing and studying are still mandated.

### *May We Change Our Genetic Chances, or May We Heal Only the Present Generation?*

The debates about testing for Tay-Sachs disease frame our discussion here. In this example, there was a clear social intervention to try to eliminate the Tay-Sachs gene from the germ line, in the sense that carrier status altered the way that marriage and procreation occurred. Testing for a variety of genetic diseases is performed by certain Orthodox communities as an extension of arranged marriages. In these arrangements, the end of the selection of partners is at least in part made to organize the best possible genetic heritage for children. Could we, instead of arranging the partners, arrange the genetic code of the partners to achieve similar ends? Is the case of germ-line alterations similar to this case? Isn't the total elimination of diseases, especially ones that are disproportionately burdensome in the Jewish population, an overpoweringly good end? In particular, when many genetic conditions were made more common because pogroms or massacres created population bottlenecks, is it not even more justified?

But further definitional questions emerge at this juncture: is the delineation of the "germ line" a useful one, or is it an early modern category that is best abandoned? Perhaps understanding some cellular transformation as "germ line" (using the rhetorical similarities to "blood lines" to make the point) and some as "somatic" when all intervention that occurs in the gametes is before the conception and creation of a new entity with a newly constituted DNA only obscures the issue. Here, we might look to how the *responsa* literature in bioethics was able to simply discard some of the categories that firmly organized the rabbinic understanding of embryology. For example, the Talmud states that "all red parts (of the fetus) come from the female, and all white parts from the male." When this is no longer supported by science, there is a range of explanations, including that biology itself was different in this period, or that the talmudic understanding was metaphorical. In this way, even formal *halachic* reasoning weighs some norms differently in light of changing scientific under-

standings.[21] Will this technology evoke a similar response, that "now biology is different"? Should this be the case?[22]

Permissibility is generally assumed by the textual tradition unless there is clear textual evidence of prohibition. Some scholars apply this principle broadly to all questions of molecular genetics, since there is no discussion of molecular genetics specifically in the *responsa* tradition.[23] However, some have objected to IGM because of its permanence. Since the modifications proposed are inheritable, does this raise special concerns? Future generations will bear the weight of our decisions. Is this *in principle* a problem? Most commentators have not found this a persuasive argument—if one would agree to the intervention on one's living child, then why not on one's grandchildren?[24] All our ideas about what will be considered moral in the future are limited by our ideas about what is moral now, but such an argument might be made for all multigenerational projects: the building of roads, the setting aside of forests, the mining of Alaskan oil. The Talmud itself, the vast churches and synagogues of Europe—all took generations to create. Must we evaluate IGM in the same way we weigh burden and benefit in these cases? Does the fact that the generations that follow might suffer unintended negative effects from our decisions render this impermissible? Like all decisions that we take in good conscience, we use our best human reason, our best understandings of science, and our good will to try to achieve good ends. Like all such decisions, every public and private action that is taken now will affect the next generation. While this is a strong argument for caution and review, it is not one for cessation of action. Shabbat ends when twenty-five hours of rest are complete. (Of course, inaction will also have its effects.) Living on the earth, making the desert bloom, and the like, all have effects that need to be reassessed by each generation. Some things cannot be "undone" (discovery of America, electricity, nuclear power, abortion technology, the birth control pill) even if they turned out to have at least mixed results.

Does the problem of consent arise—can the act be rendered in principle wrong because the next generation is "uncountable" and hence unknowable and may think the act was taken in error? IGM is very much like the many decisions that one makes for one's unknowable progeny.[25] Jews, for generations, have tried to improve the condition of their children and grandchildren, using geographical movement, preselection of spouse, arranged marriage, prohibitions on some marriages, and mandated health practices.[26] The texts of Jewish

thought do not in general call for an open future for their children with any autonomous choice available. Jewish texts teach collective activity to alter that heritage of events and constraints to which we are heir.[27] At this point, this involves taking far larger risks of deletion in the common gene pool, since we now allow for the human person, bearer of a complexity of genetic traits, to be entirely eliminated if she carries the one that we decide is diseased. IGM might allow for deletion of fewer genetic alleles in this sense. In medicine as it is now construed, we try to fix the patient rather than eliminate her. But in an earlier period, societies did just that: eliminate weak or disabled infants, or exile those with infectious diseases.[28] Theoretically, IGM might allow a greater access to particular adaptations than that which is allowed now, but it is unlikely to be on a scale similar to larger, historical genetic events. The fact that we as a species will change and shift to meet contemporary and probably Procrustean ideals of human health and function is a refinement of a continuous process, taken for the first time, only with exceedingly careful restraints if at all.

The idea that there are essential creaturely limits and essential boundaries that now define the meaning, scope, and purpose of human existence is, of course, in part a social construction. But the breaching of such limits fosters uneasiness when certain points are crossed: the change in the meaning of aging after a "normal" human life span, the replacement of human parts, the ability to reproduce past a certain age, the number of infants in a pregnancy, or the extension of life with sophisticated machinery. Since human decisions, freely made or made under socially constrained situations (war, forced migration, or famine), also deeply affect the way that DNA is transmitted to the next generation, is the intervention to remove or amplify certain DNA a difference in kind, or in precision? Such events have deeply shaped the Ashkenazi and Sephardic Jewish communities, for example. What are the species norms that need to be preserved, and how is changing this idea of what makes us essentially human, different from other medical therapy? How are other genetic interventions in the germ-line transmission impacting on this "germ line"?[29] Human persons in the Western world are large, with bigger feet, and have more robust, vitamin-enriched bodies than their counterparts in the 1800s. Humans with a predisposition to succumb to certain bacteria or women with small pelvises who would die in childbirth are kept alive and pass this susceptibility on. The chemical/industrial environment impacts on our gametes, and thus affects the "germ line" and generations hence. We compromise our genes for

economic reasons in this way. In the same way, the limits on the creaturely restrictions that have been breached systematically by medical advances also have fallen away far before genetic engineering. We accept revolutionary challenges to creaturely limits[30] and, after initial concerns about safety and efficacy, the standard FDA challenges, each medical change in our creaturely limits is ultimately first celebrated, then seen as an entitlement, becoming the new norm for community medical practice.

### *The Ontological Task of Naming*

The literature of genetic engineering suggests a further consideration. Rooted in the texts of creation is the idea that human persons are intended, specifically, to act as empiricists: observers and namers of the visible world. Adam's first praxis is naming. In classic rabbinic commentary, God interrupts God's act of creation precisely so that humans can continue the work. In reflection on why the world ends at this point (for example, with wheat neatly on stalks, but not loaves of bread on stalks, with milk nicely in cows, but not chunks of cheese), the Talmud notes, "R. Nathan said in R. Aha's name, and R. Berekiah in R. Isaac's name I AM EL SHADDAI: It is I Who said to my world, 'day' (day as in dayanu, 'enough!') and had I not said day to my world, the heaven would still have been spreading and the earth expanding to this very day."[31]

What is happening in this text? The rabbis are discussing the warrant for circumcision, an act that is profoundly not "natural." Why are men not born precircumcised? Can we intervene in nature in this radical way? Yes, they insist, in fact, it is our humanity that impels us—the principle of intervention is part of the ontology of the self. We understand the "self," in philosophic and in religious terms, as a creature with specific boundaries and obligations based on this creaturely fragility and wiliness. But all genetic speculation raises the deepest anxieties and corresponding hopefulness about the way that this notion of the self as well as the body could be altered. Jewish ethics calls for an embodied self that is extraordinarily (relative to Western secular traditions) "other-regarding." Emmanuel Levinas reminds us that this ethical stance derives its power from the constancy of the need of the stranger, the brother, and the neighbor and that this need is unceasing, only met by an unceasing duty to respond—hence the depth of the obligation in a world seen as always unfinished, beset with the constancy of illness and the reality of disabling difference. Bleich notes this in his extended commentary on this text as well. The

principle of intervention in creation extends to basic science even years removed from clinical applications. Steinberg notes that genetic manipulation, in fact, all reproductive technology, is an example of *yesh mi yesh* (something from something), not a creation of an *ex nihilo* being. It is "creation," but based on actual needs, illness, and brokenness—a fulfillment of that which is *seen as a look.* This is a principle of all *tzedakah.*

Consider this from J. David Bleich:

> It is abundantly clear that human intervention in the natural order is normatively interdicted only to the extent that there are explicit prohibitions limiting such intervention. Moreover, there is no evidence either from Scripture or from the rabbinic writings that forms of intervention or manipulation not expressly banned are contrary to the spirit of the law. Quite to the contrary, Jewish tradition, although it certainly recognizes divine proprietorship of the universe, nevertheless gratefully acknowledges that while "the heavens are the heavens of God" yet "the earth has He given to the sons of man" (Psalms 115:16). In bestowing that gift upon mankind, the Creator has granted man dominion over the world in which he lives and over the living species that are co-inhabitants of that world. Man has been given license to apply his intellect, ingenuity and physical prowess in developing the world in which he has been placed subject only to the limitations imposed by the laws of the Torah, including the general admonition not to do harm to others as well as by the constraints imposed by good sense and considerations of prudence.[32]

The mandate to heal is so strong that even apparently prohibitive texts can be circumvented with narrowly constructed, literalist readings. For example, the texts that prohibit cross-breeding of animals and mixing of linen and wool might have been seen to prohibit genetic engineering. But faced with the problem that this would prohibit genetically engineered insulin, the decisors chose to limit the *hukkim* to only the animals mentioned. In his testimony before the National Bioethics Advisory Committee on Human Cloning, Moshe Tendler concurred, noting that grafting is permitted in certain circumstances.

Bleich suggests a general principle, called "enough," based on a phrase in Genesis 17:1 in which God says "I, Shaddai" which is understood by a rabbinic word game as an acronym: *she-amarti-le-olami "dai"* (Who said to my universe "enough"?). In making the created universe, God did not complete every task (the example Bleich gives is that God could have created plants with little loaves of bread hanging from them, but did not, instead creating wheat and allowing

for the arduous bread-making process to be in human hands). In this way, we are "finishers" of the work.

## What Contextual Factors Should Be Taken into Account, and Do Any of These Prevent the Development and Use of IGM?

### *What of the Problem of Justice?*

For Jewish ethical theory, the context of the case of IGM research is the larger frame of justice in the society, and unlike the specifics of genetics much of Jewish law and codes is concerned with the problem of justice and allocation of social resources in an unjust world. Therefore, the problem of how to create a world of just order is a clear preoccupation of the biblical and rabbinic argument about the meaning and goals of a society that lives in a covenantal relationship with God. For justice to have real meaning, the civilization that is constructed will need to account for the primacy of this relationship. It is not only genetic or familial relationships, but also the problem of the stranger in Jewish thought that creates the need for a system of justice. It is the concepts of the relationships of farming and the harvest of the natural world that ground the law. All human activity of crop production is intended to produce a surplus that is meant for the poor, and the structure of the work itself allows for the surplus to be distributed fairly. We are *shomerim* for both the earth and for the poor in every harvest or use of the earth. One is not only obligated to leave the corners of the field for the poor to harvest, but is prohibited from the complete stripping of the field for one's own use for one does not utterly own it. If the first fruits are intended for a sacrifice of thanksgiving, and the next for personal use, the next collection or ripening is left for the poor, who are permitted to walk behind the harvesters to collect their due share.[33] After a generation (fifty years) the entire structure of distribution and allocation is reexamined, so that inequities of class and status linked to possession of social capital can be once again leveled. The Jubilee restores the original position, which is one of justice.

The poor are to be protected not out of a vague sense of compassion but because of how the social reality of the natural and agricultural world is structured. In fact, essential economic decisions (such as how to plant, what to harvest, and when to refrain from planting) are mediated by this consideration. Limits are placed on the entire society to ensure that the widow, orphan, and stranger are provided for with full dignity. Hence the concern for the sabbati-

cal year, in which all production is suspended to allow for the use of the field by the disadvantaged, for the harvest to be organized to allow for gleaning, for the corners of the field to be proscribed for one's own use and to be reserved for the use of the poor. Technological advances, even clever and expedient ones, cannot be permitted if persons or even animals might be unjustly used—hence the concern for the yoking of unlike animals for plowing. It is not enough, in this account, to merely yearn for a fair marketplace. All innovation of all technology begins with a selected few, be this plows, or sewing machines, or genetic therapy. All technology begins with limited access, few practitioners, and the need for a fair distribution system. Marketplace norms allow for this. Marketplace practices prohibit deception, unfair competition, but not the marketplace itself. Only unfair contracts are prohibited.

In light of technology and the marketplace, what will be important for a Jewish consideration of justice will be three issues. First, are the basic rules of a free marketplace respected, rules that prohibit deception, unfair competition, and unfairly burdensome contracts? Second, are all opportunities for the structure of production utilized to give advantage to the vulnerable and marginalized? Finally, are there ways that the gap feared by critics of genetic engineering have a prearranged reversal point, similar in intent to the return to justice of the sabbatical and the Jubilee year? It is not enough for us to consider these questions out of the context of limited access to all research funding and the lack of health care for all Americans, much less the needs of a wanting world in which infant diarrhea is still a leading cause of (preventable) death. Certain specifics must be considered in IGM. IGM research needs to be judged relative both to other competing research into diseases and well-being and to the considerations of justice noted above.

### *The Context of History*

Of all the considerations in medicine that evoke the specter of the Holocaust (Shoah), including physician-assisted suicide, abortion policy, treatment of the disabled, and research policy, none raise the issue more definitively than the idea of genetic engineering to create an altered human self. The historical link to "race" enhancement, the nomenclature of eugenics, and the marking of some as genetically "inferior" is unavoidable, and lead us to sober consideration of the role of state power in medical ideology.[34] The link between somatic improvement and subsequent power has been made in other work by many scholars.[35]

The Shoah changed the entire landscape of genetic research. While not only

Jews have reason to raise deep concern about the evil specter of genetics, Jews certainly must do so as a primary consideration. Our firmness in remembering history and our disciplined stand to avoid any chance of repetition cannot overcome all efforts at new genetic research. However, the associations with genes, blood lines, Jews, difference and danger, and Jewish history are extraordinarily strong. Critical issues such as the meaning of difference, the meaning of ethnicity, and the responsibility of a whole society to bear the vulnerability that illness and disability carry will be raised by the possibilities inherent in this technology. For Jews, the ideas of the normal have been historically used to mark Jews (Jewish blood, Jewish noses, Jewish "gaze" and gait) as different, deviant, and dangerous. Hence, mapping, marking, and altering the physicality of difference were linked to altering the social and psychological situation, and finally the mental health of the Jew.[36] Is the alteration of the diseased "type" of the Ashkenazi Jew, now used as a marker population in a number of genetic diseases, a similar case? What are the implications if that is the case? How does the specific history of the Jew and the fate of the Jewish community at the hands of a state-supported German scientific community inform our discourse on this point—a position that has been explored in a number of European countries?

### *What Do We Mean by Normality and Disease?*

In large part, our eagerness to alter the genetic material of the person prior to conception comes from a yearning to avoid the tragic choices faced by parents who know prenatal diagnoses and are faced with the dilemma of abortion. In such cases, we focus on conditions that are the most disabling, are incompatible with life, or have short and brutal courses. But what are we to do in the case of other types of disease, such as late-onset diseases with milder courses? One such example is Gaucher disease, far more prevalent in the Ashkenazi Jewish population than in the general population, which can have mild or severe forms and can be treated with (expensive) medical therapy. At what point, we are led to ask, are interventions "medical therapy" and at what point are they atheistic, or amplification? What does calling germ-line intervention a medical therapy imply for us? Linked to this issue are haunting questions about the nature of such alternations. One line of reasoning asks about possible uses of carrier status of such genetic diseases or alternations. Could there be a protective feature to the carrier status for genetic disease that is more prevalent in the Ashkenazi Jewish community?[37]

Further, permission to alter the physical body has been linked to the way that the "disfigured" body has affected the mental health of the person—connecting the intervention to a medicalized end. Will this be the warrant for genetic intervention? If this is the case, then a far larger window of possibility might open for the use of this technology. Like gene sequences themselves, the future is not predictable or stable: the qualities we see as problematic at one historical period might be seen in another as valuable. But it is unlikely that fatal or severely restrictive diseases that involve progressive muscular degeneration or cognitive impairment would ever be valuable; neither smallpox, nor anthrax, nor polio, for example, is considered a valuable part of the natural world.

Over all of this technology lies the complex social influence of the marketplace, in particular, the pharmaceutical industry. At the present time, the medical model supports the ideological construction of the self as a basically intact entity, besieged by alien germs that need to be confronted with drugs to kill them (antibiotics), or as a self merely lacking a chemical that could be equally nicely supplied by a drug company (insulin). Hence, the marketplace endeavors to supply these commodities. But if the self qua self can be altered to change the underlying proteins that control the immune system, for example, or the production of enzymes, then externally offered drugs will not be needed daily. Such a shift represents both a significant marketplace change and a significant change in the meaning of the self. Further questions of context and norms arise: how will aesthetics, physical progress, and advantage create a climate of approval for genetic changes that allow or disallow regulations?[38] Will this "ill self" be seen as a burden, and to whom? Can the legacy of this language be understood as anything other than dangerous?

## What Purposes, Techniques, or Applications Would Be Permissible and under What Circumstances?

In the religiolegal system of Judaism, the question of permissibility also concerns the technical aspects of the complex physical manipulation of women's bodies in particular required for IGM. Here we will need to address questions of informed consent; the use of advanced reproductive technology (ART) such as in vitro fertilization (IVF), cell harvest, use of third parties, extracoital reproduction, and the perimeters of the family; contracts; the effect on the character of the researchers; and the issue of limits on the applications and participants.

### *Can Consent Be Fairly Obtained?*

Informed consent is at the heart of all medical intervention. What separates the abuses from ethically appropriate research is the consent process, involving repeated and careful disclosure, control of the information, confidentiality, and the ability to withdraw from the process at any time. Families seeking IGM would be at first few: they are by definition exceptional, and exceptionally desperate. Hence, the genre of questions that will inevitably emerge from such a practice will be driven by a sort of desperation that evokes (especially in the Jewish tradition) a predictable response, a response of rescue. In light of such questions, can consent be genuine?[39]

Further issues of process surround the problem of parental decision making. This problem is extended and potentiated by the longevity of germ-line decisions. Here, one is making decisions not only on behalf of one's own child, but for all subsequent generations of children. Such decisions about health, illness, and normalcy are culturally constructed (e.g., the "pathology" of short stature) and subject to change.[40]

### *How Will the Process of Manipulation Affect the Researchers Themselves?*

How would the performance of the act of "harvesting" aborted fetal cells and all that this entails affect the scientists involved? What must be considered to protect the researcher from becoming indifferent to the human tissue involved in the use of the blastocyst? How can research scientists, by design removed from patients to protect the informed consent process, still act as if they are healers, motivated in the ways that must inform and direct the research? How will the significant monetary incentive affect this commitment?

### *The Inevitability of Error and the Problems of Unintended Consequence*

At this time, all genetic engineering articles begin with caution. Cloning experiments have resulted in spectacular failure and only rare successes, and somatic genetic research is still in its earliest stages. Human IGM research is nearly entirely speculative. Even when the technological issues are clarified, the very gesture of conventional medicine, much less genetic medicine, is inherently and inevitably fraught with error. Our understanding is primitive and in-

complete, and the complexities of the interaction between DNA, expressed proteins, and the environment is little understood. Much of the secular discourse has been directed toward the problem of safety and efficacy.

Genetic variation is at this moment not completely understood, predictable, or stable; rather, the genetic coding of the proteins that direct living processes within the cell are always mutable. In fact, in some of the most devastating genetic disorders (a class of diseases that include myotonic dystrophy and fragile X syndrome), the effects of the disease worsen in each generation as the once benign genetic pattern is copied into ever larger sequences. If we turn from the technology, we might also be turning from an obligation to save future children from afflictions. How safe does an intervention have to be before it is attempted?

Finally, the unintended consequences of even successful genetic intervention are little understood. We can know for certain only the history of such consequences and history may or may not repeat. All medical advance has led to significant shifts in demographics, historical forces, and social power arrangements.[41] When Steptoe and Edwards first advanced the idea of IVF for purposes of reproduction, initial Jewish British reaction warned against the possibility of creating monster children, or children who would suffer later effects of intervention thought to be lifesaving at the time. For the Jewish American community, which was heavily affected by the "lifesaving" reproductive intervention of the 1950s–1970s, diethylstilbestrol (DES), the lessons were particularly acute.

### *The Compromised World of the IVF Clinic*

A different sort of *halachic* concern is raised by the physical process of the research. The process of IGM would involve several steps. In the most likely scenario,[42] an individual carrier of a disease would be identified and produce an egg for harvest. The egg would have to be fertilized outside of the womb in vitro, perhaps using intracytoplasmic sperm injection (ICSI) techniques for precision, and the resulting fused cell, now the zygote, would be examined using prenatal diagnosis techniques, in which the individual DNA of the cell is tested for the targeted diseased gene. The gene would be "spliced" and replaced with a healthy copy of the gene. The altered cell would then be allowed to continue cell division to the embryo stage, and would be eventually reimplanted.[43] At each point the origin of the genetic material presents *halachic* problems, including: Can we use drugs to stimulate ovulation?[44] Can we harvest eggs from a woman for IVF?[45] Under what conditions can donor sperm be collected and

used?[46] Can we implant an IVF embryo?[47] Can we use a surrogate to gestate the embryo to term?[48]

## What Procedures, Structures, Involving What Policies, Should Be Used to Decide on Appropriate Techniques and Uses?

Do we have an obligation *to pursue* this research? Or do the *halachic* considerations lead us toward supporting a ban on genetic research on human embryos at this time? It seems clear that while there are no *halachic* principles that forbid genetic engineering, the social contextual and safety issues do not allow for human applications of the science at this time. What would this mean for public policy? What if we understood the Jewish position as mandating this research in an uncertain political climate? Would our stand imply an activist role for our leadership? Does a general obligation to "heal" include all possible avenues, and are we obligated even if the consideration of justice would mandate other research be pursued? If the activity is prohibited for Jews, might it still be permitted for other persons, as is the eating of pork or the grafting of trees?

### *How Best to Control the Marketplace Pressures Driving Technology?*

The field of assisted reproductive technology is marked by its unrestrained use of the marketplace. Without proper oversight, fees, contracts, the standards for clinics, and the lengths that people are permitted to pursue are unlimited. With new technology that will powerfully extend human life and potentially alter moral meaning, can we offer ethical guidelines to inform policy in this arena? How can the use of contract law, or the rabbinic prohibitions on marketplace exchanges, or rabbinic limits on the instrumental use of the body of another be used to regulate this arena? In other words, what rabbinic norms that are found in sources removed from medical consideration, but related to civil law and justice, might be mobilized to assist our thinking about the just use of technology?

### *Creating a "Civic Witness": Public Moral Agency for Genetic Research*

In a plural civic society, Jewish ethics can contribute to the discussions on genetic research in two ways. The first is to define the limits on how Jews ought to use genetic knowledge, and the second is to model a response for the whole society. Claiming the latter allows a wider response. One must do more than simply describe classic commitments and familiar texts in Jewish medical

ethics (saving life above all else, the duty to heal, the partnership with God to act as stewards in the world, or the general mandate to produce children), for these commitments allow nearly all technology to be described as lifesaving in a general, genial way.

For the vexing problem of regulation, I suggest that one might use as a model the discursive debates of the Jewish textual tradition itself in which the discourse serves as both interpretive and regulatory community. Certain caveats apply. Scientific freedom is not a right but exists in the context of a society that creates obligations on research, one similar, I would argue, to all human production. Curiosity and the pursuit of research is a concomitant part of how language and perception shape what we find compelling work, but the research must be conducted with attention to justice, to the distributive manifestation of the work, and to the effect, in particular, on the most vulnerable. Open reflection must be allowed on the process and on the outcomes, as is the case in all other venues of the human search for knowledge. Basic research can in this way be considered unfettered and intrinsic to the human occupation of the earth by Jewish law. However, there must be a corresponding duty to evaluate effects and social consequences. Since societies pay for the work of research,[49] they have an obligation to know, understand, and reflect on the work that a society's labor funds. Jewish tradition, unlike some other traditions, does not have a history of scientific regulation. Scientific advances present a legal puzzle to be solved, but not a theological heresy, in that there is no "unpermitted" secular study. Science, rather, changes the understanding of the world as perceived, allowing an embrace of technology as it proves useful and not harmful.

Much new work needs to be done. Recent reflections by Robert Gibbs suggest a turn toward the law of repair of sacred texts that have been damaged as a source of how we might understand how Jews think about both saving and yet restoring to a norm even sacred words. Such creative use of the Law is an example of how thoughtfully we will need to explore our tradition in order to understand its distinctive contributions.

With such caveats, the Jewish discursive methods can be seen as largely enthusiastic for the fullest embrace of basic research within a larger quest for justice and public accountability. It is my responsibility to represent such texts fairly, to urge a national debate that stresses an openness to both complexity and to imperative, to caution and to healing, to curiosity and to care. The miraculous knowledge is not only in our advances, but in our ability to stop,

reflect, argue, and agree before we continue on the journey to the next days of creation. A further and direct task of the Jew is to *shomer Shabbat* (observe the Jewish laws of the Sabbath calling for rest) and what that task of *shomer* might mean in this context. I would argue calling for a *Shabbat* in genetic research, not a ban. It would limit the kind of work we permit; perhaps Temple building is a good metaphor. It would be a specific period of time, and, of course, study and direct healing of a specific other would be our duty.

The future is both uncountable and unknowable, but it is our *responsibility,* of that we must be certain. We are answerable to a world we cannot know, to every star, every grain of sand, every child who will come.

NOTES

1. In the United States, the Recombinant DNA Advisory Committee (RAC).

2. Laurie Zoloth, "Born Again: Faith and Yearning in the Cloning Debate," in *Cloning and the Future of Human Embryo Research,* ed. Paul Lauritzen (New York: Oxford University Press, 2001).

3. And even for a sense of authority beyond available textual sources. As in Rabbi Josef Shalom Eliashav, who has been cited as stating that cloning is "against the ruach (spirit) of Torah, apparently in reference to Nachmonides theory of 'natural law' implied his comments on Va-yikra 19:19." See Yoel Jakaovitz, "Cloning and Its Challenges," *Torah U'Maddah Journal* 9 (2000): 195.

4. For the purposes of disclosure, this author is a member of a Modern Orthodox community.

5. Of importance to note is that Jewish law, unlike American secular law in which something is permitted or prohibited, describes four categories for possible action. An action may be permitted, or unpunishable under the *halachic* code, but morally undesirable; an action may be permitted and desirable; an action may be prohibited (even if desirable); or an action may be permitted by Jewish law, but prohibited by the secular state (and thus be permitted, since "the law is the law of the land, dinah d'malchut dinah").

6. In general, unless the act in question involves idolatry, adultery, or murder, any moral gesture can be evaluated, including the permanent alteration of the genome.

7. Kenneth Waxman, "Creativity and Catharsis: A Theological Framework for Evaluating Cloning," *Torah U'Maddah Journal* 9 (2000): 188–93.

8. Talmud Balvid Sanhedren 65a.

9. It is a subject of a current novel by Marge Piercy, *He, She, and It* (New York: Knopf, 1991). The tales recur in the eighteenth century and in the texts of the *responsa* literature (Zevi Ashkenazi, She'elot u-Teshuvot, no. 93). In one such text, the question is raised about whether the Golem can be included in a prayer quorum, or minyon. At stake is the issue of murder. If the Golem is a man, then is it not killing to "return him to dust"? (One thinks here of the legal cases involving the destruction of embryos.) The

text resolves this in an odd way, not by claiming the humanity or countable status of the Golem, but by decrying the waste of a creature with "a purpose."

10. John Loike, "Is the Human Clone a Golem?" *Torah U'Maddah Journal* 9 (2000): 238.

11. This entire section is from Laurie Zoloth-Dorfman, "Mapping the Normal Human Self," in *Genetics,* ed. T. Peters (Cleveland: Pilgrim Press, 1998).

12. Joseph Soleveitchik, *Halachic Man,* tr. Lawrence Kaplan (Philadelphia: Jewish Publication Society of America, 1983), 99.

13. Ibid.

14. Waxman, "Creativity and Catharsis," 191.

15. Avraham Steinberg, "Human Cloning: Scientific, Moral, and Jewish Perspectives," *Torah U'Maddah Journal* 9 (2000): 199–205.

16. Yitzchok Adlerstein, "Scientific Advance and the Jewish Moral Conscience," *Torah U'Maddah Journal* 9 (2000): 184–87. In this article, Adlerstein recounts the support of the medieval rabbinic authority, the Maharal, for this idea.

17. Steinberg, "Human Cloning," 213. Citing here Rabbi Shlomo Zalman Auerbach and Yehoshua J. Neuwirth.

18. Hence, the concerns have been outcome driven. But in looking at the process, contemporary rabbinic response has been largely theological, and not legal. Discussion refers to the mandates of Genesis 1–3, in which issues of creation, stewardship, and limits are described.

19. "Cloning in Jewish Law: A Symposium," *Torah U'Madda Journal* 9 (2000).

20. Ibid.

21. Baruch Brody, in unpublished remarks, Houston, January 2001, "Genetics and Human Freedom."

22. Rather than a point of principle, class Jewish method is a type of casuistry. Does this act differ in principle from other actions with similar moral features (a casuistic question)? In many ways this is similar to other dramatic understandings of the etiology of disease and our subsequent intervention. For example, the inoculation of the British with attenuated smallpox was an intervention based on the new understandings of disease. It was blocked in France by the College of Theological Studies when the king of France took it there for consideration. The theological argument was that this intervention interfered in Providence and was not to be permitted (until the death of the king from smallpox, after which the theological considerations were changed). But once the safety of the procedure is assured, no principle proscribes such technological advances as the smallpox vaccine, anesthesia in surgery for childbirth, or computers. As we learn more about God's universe, we can act more efficaciously to live and flourish in the universe. Hence, actions that do not destroy the earth and actions that allow humans to be in relationship to God (and to perform the mitzvot that are appropriate to them) are morally permissible and are to be encouraged. The question is: will this intervention change the essential character of the human who is in covenant with God?

23. Moshe Tendler, testimony before the National Bioethics Advisory Commission on the Ethical Considerations of Cloning, 1999.

24. Eric Parens has speculated that alteration in the future is based largely on our conceptions of morality in the present.

25. Circumcision is a clear case, but there are many others: the decision to live in Is-

rael or the United States may affect one's progeny for generations. Any decision we make forecloses options.

26. But some have argued that IGM differs in kind from this sort of personal decision, since it is an intervention in a larger human endowment, or a human "gene pool." This argument constructs a sort of universally accessible "pool" or endowment to which all have equal access. Such a notion is a linguistic fiction. It also is a reification of the idea of a "nature" that is always held as somehow sacred—not a notion that arises in Jewish sources. Nature is not seen as inherently moral, or innocent, or good. Nature is not "sacred." The natural world is not "the place" where the holy is to be "found." Human persons are not apart from nature, nor are the manipulations or adaptations seen as extrinsic or abusive of a discrete "nature." What makes us human is not our genes, but our social interaction, our relationships to God, community, and history.

27. Further, work of Juengst suggests that such a premise is based on linguistic confusion. In a sense, it is true that I as a human have a sort of participation in a species that contains Joe DiMaggio (the genes for stronger arms and faster muscle synapses than mine) and Michael Jordan (the genes for height bigger than mine). I am also a participant observer in the gene pool that includes tragic genetic diseases, such as those that killed Woody Guthrie and Lou Gehrig. But we move as a species, and have for generations, toward trying to control the perimeters of such a heritage. Selective medical abortion is the major way in which we do this now. Further, we inherit a world in which we commonly share smallpox and river blindness, diseases caused by parasites that we intend to destroy totally if we could (this sort of nature we consider less than sacred).

28. There is a sense (noted fully by the disabled community) in which selective medical abortion is a similar act, elimination for the purposes of eugenics in a way that will alter the genetic heritage. See Chapter 11 in this volume. In classic Jewish considerations of intermarriage, what is key is conversion to faithful observance, not the quality of the DNA. In fact, one is prohibited from disparaging the convert on the basis of her or his family of origin, and is enjoined to complete acceptance. The idea here is that human moral behavior is more important than the gene "pool."

29. One thinks here of the way that ICSI, the selection of a particular sperm to be injected into an particular egg, alters spontaneous fertilization.

30. Here sits the ethicist, wearing glasses, having had children in her 40s, after having visited her 80-year-old father after his angioplasty.

31. Midrash Rabbah 46 2.

32. Bleich, *Tradition.*

33. See, for example, the Book of Ruth.

34. In many ways, the gross indignities of the state's use of genetic technology seem less a hazard than the temptations of medicine itself.

35. Sander Gilman, *The Jew's Body* (Bloomington: Indiana University Press, 1995).

36. Zoloth-Dorfman, "Mapping the Normal Human Self."

37. The one most noted is the possible link between Tay-Sachs and tuberculosis.

38. Consider here the link between funding and mandated testing for genetically borne diseases of the neonate, PKU, and the fact of a particular legislature with a child bearing the disease.

39. Other process factors first considered included: Is IGM adultery? In the first

years of advanced reproductive technology, some argued that IVF techniques that might be a part of this activity border on adulterous relationships (the fertilization of the egg by sperm that is not conjugal). But most sources argued to the contrary, and this issue has been largely settled in the *halachic* literature. Finally, is IGM murder? The intent is far from this, and in fact is specifically life enhancing. Embryos created in vitro are not considered technically human until they are implanted, a point that all Jewish commentators agreed on, and are not ensouled with particular moral status until the fortieth day postconception, but are "as water."

40. One can think here of the way that the Victorians "saw" a healthy female body, for example, and consider the implications of genetically altered female torsos if constructed in that era.

41. Jared Diamond, *Germs, Guns, and Steel* (New York: W. W. Norton, 1997).

42. Another description of the process would involve the administration of an external agent (and advocates of HGRT have noted that this occurs now in the process of radiation exposure, certain chemotherapies, and somatic cell therapeutic interventions as an unavoidable side effect) that would affect the gametes of the parents whose genetic structure we intend to alter. They then would reproduce a child in the usual way (!), and that child would carry the altered DNA structure from the altered gamete cells that were his origins.

43. In a woman (the woman could be the same one that from whom the egg was collected or could be another woman entirely).

44. This issue has been debated in early questions about the development of ART and resolved. Medications to stimulate fertility (mandrakes) are spoken of in biblical literature approvingly. The problem of biblical infertility is resolved on the spiritual level, but there is no prohibition against the use of all medical intervention that can help a couple achieve the commandment to raise at least two children.

45. Eggs are part of a body, not having the status of fully moral entities, even when fertilized in vitro, since before forty days, the embryo is "like water."

46. Here we find the first problems in the use of ART as a part of the process. Of concern are two issues: Is it adultery if the sperm of another man is used inside a woman's body (as in artificial insemination?), and what if the offspring of two families might by chance marry—could a prohibited marriage occur? (Prohibited marriage would include marriage to one's half-sibling, a remote but interesting theoretical possibility.) For this reason, some Orthodox rabbinic sources prohibit the use of donor sperm for artificial insemination. Even for the use of the husband's sperm, or in some cases, the use of a mixture of sperm sources to meet the *halachic* requirements, there are special considerations—sperm is not to be wasted (the sin of Onan), so elaborate collection devices have been created to allow for coital stimulation and collection of sperm. But on this point there is sharp disagreement, even among Orthodox rabbinic commentators. ("You cannot commit adultery with a hypodermic syringe. Even if a woman uses donor sperm against the will of her husband, it has no consequences for the child.")

47. In this phase, as in several of the others involved in ART, rabbinic authorities have used the general pronatalist slant of the tradition to permit (but not require) this type of intervention. Noncoital pregnancy permitted? For Rosner, Tendler, and others, the issue of interest is the status of the child, since issues of parentage are key in Jewish

law. (Children born out of adulterous unions do not have full Jewish religious citizenship and are not permitted to marry except to other such children.)

48. Several commentators have noted that little in *halachic* tradition prepares us for such a question. Some advocate a turn to the biblical narrative. But is the use of Bilpah and Zilpah as surrogate wives a felicitous situation? There is nearly unanimity on the dangers of such a course. Gordis, Dorff, Jakobowitz, and Gellman (from all three movements) agree that surrogacy creates problems of intractable social injustice, raises technical issues of slavery, and has disturbing implications for family unity. Here a fruitful investigation of the business ethics of unfair contracts ought to be undertaken as we continue this sort of process investigation.

49. Either directly, via taxes, or indirectly, in the use of products.

CHAPTER FIFTEEN

# Parental Liberty and the Right of Access to Germ-Line Intervention

## A Theological Appraisal of Parental Power

Sondra Wheeler, Ph.D.

What does the legal and moral right of autonomy imply about a right to have access to the technology of germ-line genetic intervention to alter the inheritance of one's offspring? Before addressing this question, it is necessary to be clearer about what kinds of autonomy claims are thought to apply in this realm. This requires disentangling several related but distinguishable concepts. Phrases such as "the right to reproduce," "reproductive autonomy," "parental autonomy," and "parental liberty" have been variously used and understood in this and other debates about the resort to reproductive technology. I am going to define and use two of those terms to make a distinction between two different loci of claimed freedom and two different rationales for granting and protecting that freedom. From there, I will be in a better position to offer a theological appraisal of claims about the legitimacy and the limits of the power that parents exercise over their children. This will provide the basis for a normative argument about the nature and the reach of appropriate liberty, and what it suggests concerning a putative right to access to this technology.

## Reproductive Autonomy

Linked most often with reproductive choice, the term *reproductive autonomy* has achieved much of its currency in the context of the ongoing debate about abortion. It is understood as the individual's right to freedom from interference or constraint in the exercise of his or her reproductive capacity, including choices about conception, contraception, and termination of pregnancy. It has been invoked to oppose coercion in both directions, that is, as a right to refuse contraception as well as the right to have access to it, a right to freedom from forced abortion as well as a right to obtain a desired one. Reproductive autonomy is usually justified as part of the defense of bodily integrity, the right to determine what happens in and to one's own body, or as a right to liberty and privacy in making intensely personal decisions about whether or not to have a child.

Even those who recognize the moral gravity and the social consequences of such decisions are loath to impose any direct constraint upon them. Although decisions about parenthood may be and often are made irresponsibly, it is generally thought too massive and fundamental an interference with basic human activities and functions flatly to impose a social judgment about whether or not a couple should conceive and carry a child. Thus, Cynthia Cohen in an unpublished paper on this topic poses the hypothetical case of parents who are homozygous for a fatal genetic malady, but elect to conceive a child in spite of the certainty of its affliction and early death. Even here, she notes, while one may judge the couple's decision immoral, actual legal constraint of their liberty to conceive such a child would itself be morally abhorrent. For the purposes of the following discussion, I will accept both this argument and its rationale.

I want to note a few features of the concept of reproductive autonomy. The first is that the claim of reproductive autonomy has its foundation in the individual and his or her personal freedom, in the privacy of decision making about basic life goals, and in the integrity of the body. This is true despite the biological fact that the actual power to procreate inheres only in pairs of human beings. The individual locus of this autonomy is evidenced by the fact that the state may not constrain a woman who decides to conceive a child by means of an anonymous sperm donor, or who conversely decides to have an abortion without her partner's consent. (The picture is a little cloudier for men who wish

to become parents on their own. Given biological constraints, in practice this must involve either the active involvement of a willing partner who then has her own parental duties and claims, or the use of a donor egg and implantation in a surrogate womb. This latter option presents additional public policy issues that are more problematic.)

The other notable thing about reproductive autonomy is that it is almost entirely a negative liberty, a right to freedom from interference rather than a claim to positive help. The law does not contain any provision to include infertility treatment beyond routine diagnostic services in publicly funded health care, nor has it assumed that we have a right to the cooperation or assistance of others in exercising our reproductive powers. This negative character of reproductive autonomy may help to explain why we feel we have a duty to protect even immoral choices, at least in the limited sense of not coercively preventing them: people are free to make a large number of bad choices without being forcefully interfered with. Of course, as a society we *do* reserve the right to force individuals who make such choices to bear some of the consequences thereof, as when we compel absent or irresponsible parents to pay child support. But the freedom to make choices about your own bodily life and powers and their use is simply too close to the bone, too central to what it is to be human, to be outwardly constrained except for the most compelling of reasons. Thus, on one hand, the barrier to interference raised by reproductive autonomy is very high; on the other hand, the range of the freedom it protects is correspondingly narrow.

## Parental Liberty

To this strong legal and moral claim to freedom from interference in the realm of decisions about whether to conceive and carry a child, I would like to contrast a distinct kind of liberty that has a quite different foundation. This, which I shall call "parental liberty," is not based on the personal freedom of a single individual as such. This liberty, and social support for it, is grounded in the significance of a certain, crucial relationship whose importance to individuals and to social groups is hard to overstate. It is the relation between parent and child.

To begin with the personal significance, strong and effective ties between parents and children are essential for the successful nurture and formation of individuals. Nothing is more critical to child development and welfare than the

presence of a consistent, powerfully invested caretaker who provides not only protection and physical care, but also the context for psychological growth and stability. It is within this primary care relationship that both the ability to identify the self with others and the ability to differentiate the self from others are formed. Those who are deprived of this intense relationship, in which the young child has an individual personal identity ascribed, affirmed, and reflected by an attentive caretaker, may fail entirely to develop a stable sense of self. The absence or failure of such a relationship is a devastating loss in a child's life, whose effects are unpredictable and far-reaching. In the overwhelming majority of cases, this crucial relation is established with the child's parents.

But the parent-child relationship is not just a matter of individual well-being. The broader community also depends on this structure to accomplish the enormous, long-term, and labor-intensive tasks of child rearing. These include material support, daily physical and emotional care, basic education in language and culture, and socialization into the customs and norms of the community. There is no failure so costly to a society as a failure in this primary arena of nurture and formation, none so difficult to repair or compensate for as the breakdown of this most fundamental social relation. Those who do not learn to bond and empathize with other human beings through this interpersonal connection, who do not learn how to function within the group of which they are part, are at best handicapped in their social relations. At worst, they are dangerous.

Because of the scope and significance of the parental task, parents have very wide liberty in this undertaking, and the power they wield in the lives of their children is enormous. Since their purview extends beyond providing physical protection and nurture to providing a structure of values and a coherent view of the world, parents also have authority to construct the moral and emotional world in which their children live. They may allow greater or lesser freedom to depart from familial norms and practices. They have the support of the society in the exercise of this authority, and broad latitude to determine their minor children's property, medical care, education, religious observance, recreation, outside influences, friends, clothing, and even how they may wear their hair. Nor is social support for parenting merely negative and indirect. Parents receive extensive, positive social support in the furtherance of their parental role. This ranges from legal defense of their decision-making authority, to tax exemptions and tax credits for the material support and care of children, to publicly funded nutritional, educational, and medical services. In all of these

realms, how and to what extent such public resources are used remain matters of parental discretion.

But having laid out the great range of parental decision-making power in regard to their children, it is essential to remember why this power is protected and what it is *for,* for it is not arbitrary but directed to an end. The end is to foster, facilitate, and protect the vital role of the parent, directly for the sake of the child who is to be cared for, and indirectly and secondarily for the sake of the wider society into which this child will enter when grown. Both legally and morally speaking, the power and liberty of parents is substantive and positive, but it is liberty *for* their children, not simply liberty over-against them. Positively, it is the liberty to provide them a full and appropriate nurturance into an adult way of life.

The human goods into which children are to be nurtured are variously construed, and any model of mature well-being toward which parenting may aim incorporates substantive and contestable judgments about truth and value. Therefore, parents do and must have the liberty to make judgments about what is good for their children that not all members of the community would ratify. However, those judgments are not by any means completely unconstrained. Even in our individualist and democratic society, which cherishes autonomy and private judgment to a high degree, the education of children is compulsory until they are sixteen (although the particular character and setting of that education may be left to parental choice within wide limits). Similarly, parents must provide needed health care for their children, and even the claim of a religious privilege will not protect them from charges of abuse or neglect should they fail to do so. Physical mistreatment or neglect of children can make parents subject to prosecution and imprisonment, as can sexual abuse or even extreme verbal and emotional abuse. Parents who fall significantly below social standards of adequacy in the fulfillment of their parental responsibilities can have their liberty curtailed, subjecting them to monitoring and supervision by society's agents. Continued failure to exercise parental authority in a way that provides for children's basic welfare can lead to the court-ordered loss of custody, parental rights, and even the privilege of visitation. In short, in law as in morality, the comprehensive liberty that parents enjoy in the care and rearing of their children is not only justified but also *limited* by the ends that relationship is intended to serve, both for individuals and for society. When it fails to serve or directly contravenes those ends, parental liberty can be forcibly terminated.

## The Liberty to Nurture

Thus far I have spoken of reproductive autonomy and parental liberty in light of law and social practice in Western democracies, and in ways that do not depend on full-blown philosophical or religious accounts of human goods and human purposes. This has been sufficient to display the difference in the foundation and scope of these two different kinds of freedom, and in the grounds for curtailing their exercise. In contrast with the negative right of reproductive autonomy, I have argued that parental liberty entitles one to more positive assistance, over a wider range of related activities. At the same time, parental liberty finds its ground in the significance of a relationship rather than in the rights of the individual. Thus, it is both supported and limited *for the sake of* the goods to be provided in that relationship, especially the good of the children in regard to whom this liberty is exercised. When the interests of children and the secondary interests of society in their nurture are not served by parental liberty, it can be limited or removed. The parental liberty that is socially recognized and protected is not neutral, but directed; it is the liberty to nurture, and not merely the liberty to control.

Now I want to supplement this understanding of parental liberty with an account of the moral character of parenting shaped by Jewish and Christian doctrines of the person, and related conceptions of the weight and limits of human "belonging" within families. Within this theological framework, I wish to offer a "thick description" of some of the basic features of parenting that enable us to nurture human beings well. I will then be in a better position to offer a preliminary assessment of a claimed right to have access to germ-line genetic intervention grounded in parental liberty, and to consider whether and where it might apply.

The first point to make is that Christians and Jews receive their children as gifts of God, as temporarily dependent and entrusted to their care, but also and from the outset as fellow humanity. This marks the child as possessed of the full dignity belonging to any human being. This dignity is to be recognized and honored in the child despite her or his lack of the functioning capacities that secular accounts frequently posit as the ground of respect for persons. From a theological standpoint, it is not present or even future bodily capacity but *creation and eschatology* that provide the decisive grounds for the reverence that is due to human persons. This child has the same source and the same destiny

as its parents, and joins them as the beloved creature of God, made for the union of knowledge and love with its Creator that is the destiny of every human being. This recognition forms the basis for a kind of fundamental equality between parents and child that remains despite the dramatic asymmetry of their relationship. Children are, on this view, subjects in two senses of the word, in that they are never merely objects in relation to parental desires or goals, and they are simultaneously subjects in relation to God who is their sole sovereign.

Coexisting with the dignity of human creation are the imperfection and contingency and vulnerability that are part of embodied creatureliness. Our children are, with us, subject to accident and illness and chance, to the random events of mutation and bodily defect, and to all the suffering that these may impose. Responding compassionately to such events falls within the scope of our obligation to provide care, to relieve suffering, and to manifest toward our offspring the patience and loyalty that God manifests toward us in our weaknesses. Similarly, intervening to prevent or to ameliorate the effects of accident and illness is consonant with the human mandate to exercise dominion over creation, which is understood as modeled on God's care for the world which honors and does not violate it.

However, that last provision is crucial, for our "dominion" is a derivative and delegated authority, exercised as God's agents and not as God's replacements. We are not the creators of the fellow creatures on whose behalf we intervene, and we do not determine their nature or their flourishing: we merely discover and foster it. Nowhere is this reservation more critical or in more danger of subversion than in our relation to our children. It is essential for us to remember that as parents who are not creators but only procreators, our children are not *for* us and are not "ours" in any ultimate sense. They are not our possessions or our projects, nor are they our responsibility in so sweeping a sense that they can permanently be deprived of liberty or responsibility in the name of our exercise of care. They come at once from us and from beyond us, and we accept both possibility and limit in shaping their existence, both inwardly and outwardly.

Finally, a constitutive feature of the relation between parent and child is that it is not simply a voluntary personal commitment, such as the one we make to a spouse or to a friend. We are committed to our children as ours before we ever lay eyes on them, and one of the decisive facts about parenting is that when we enter into the relationship, we don't know who is coming. While we may choose to have a child, we rather welcome and discover than choose the particular child. We receive and live out our responsibilities toward our children simply because

they are ours and we are theirs, and that is enough to bring us to welcome and cherish and protect them, whoever they turn out to be. It is this unreserved and uncalculated commitment to accept and love the children we are given that makes the relationship between parent and child so unique and so central a picture of our relationship with God. In this most basic and essential of all social relationships, we see the nearest human analogue to the divine charity which loves each individual in her or his particularity, but universally and without conditions. It is concern to preserve this crucial virtue of parenting that animates some of the most forceful critiques of germ-line intervention.

## Access to Germ-Line Intervention and the Liberty to Nurture

Is it possible to find in this positive and theologically grounded version of appropriate parental liberty grounds for a right (or at least a permission) to modify intentionally the genetic inheritance of one's descendants? On the one hand, does this account of the personal and social goods for whose sake we protect parental liberty support the use of such technology? On the other, is such intervention compatible with the thicker, theologically informed description of the internal character of parenting as a practice in which one creature nurtures another who remains fundamentally an equal, in primary relation to God? Unsurprisingly perhaps, it seems to me that the answer is "possibly," but the list of conditions and qualifications that would have to apply is long, and may be impossible to fulfill.

To begin with, society's interest in parental liberty arises from its interest in the well-being of children in general, and includes future as well as extant children. This would impose a very high bar in terms of the safety, reliability, and effectiveness of the proposed intervention. Moreover, this standard must be applied not only to the proposed recipient, but also to all his or her descendants. It is a matter of fierce and presently unresolved debate whether the safety of such interventions can ever be established over the extremely long run required to justify them. Reservations about this possibility must be taken seriously. However, it must also be noted that an intervention to correct a genetic defect like that leading to Tay-Sachs disease or Lesch-Nyhan syndrome would have to be seriously deleterious before it could be thought to impose a greater burden than the disease it prevented. Conversely, genetic alterations whose contribution to basic health and welfare is less clear and compelling than these would face a heavy burden of proof that it might be impossible to meet.

At the next level of justification, if parental liberty is recognized and honored for the sake of the well-being of children and only indirectly that of the wider society, any proposed intervention must pass the tests of being undertaken directly and primarily for the sake of the child rather than the parents or other parties. Therefore, the motivation for the intervention as well as its consequences must come into the assessment. The correction of demonstrable defect and the prevention of serious, identifiable disease would weigh very heavily as being clearly in the inheritors' interest, and therefore belonging properly to the parental task of fostering basic well-being. Conversely, the selection of subjectively or culturally desirable traits would receive less weight as being related more ambiguously to the child's welfare and more obviously to parental satisfaction or social productivity. I will return later to the issue of whether and how such an implicit distinction between therapy and enhancement can be maintained with sufficient clarity to inform public policy and regulation.

More complex and difficult still is the matter of weighing whether germ-line interventions are compatible in principle with the moral character of parenting as Jews and Christians are led to understand it. I have identified three aspects of parenting that arise from central theological affirmations about the nature of human beings and the character of their relationships, each of which has some bearing on the prospect of germ-line modification. The first is that the child must be recognized as fellow humanity, due a full measure of respect as an equal whose nature and dignity are rooted in his or her creation by God. This essential equality rules out any treatment of the child as primarily a means of parental fulfillment, subject to fundamental manipulation in accordance with parental desires. The second is that the child is recognized as an embodied creature subject to illness and accident whose vulnerability to suffering calls forth appropriate protections and interventions to support its well-being. This is accompanied by the caveat that we protect and intervene as creatures charged with nurture and protection, not as beings who can assert unqualified liberty vis-à-vis other creatures. The third point is that central to parenting as a moral practice is the recognition that we receive and welcome our children as they come to us from God, rather than selecting or constructing them in accordance with our own preferences. The unconditional commitment to our offspring whoever they turn out to be is critical to the character of this relationship, and precludes the establishment of criteria by which we will embrace or reject loyalty to the children born to us.

These commitments pull in both directions. If religious reverence and fun-

damental loyalty preclude making the child-to-be the object of arbitrary manipulation in accord with parental desires, the recognition of vulnerability and the commitment to protect and nurture warrant positive actions when the child's well-being is threatened. The questions in view include both what constitutes arbitrary and therefore offensive power *over* a child, and conversely what kinds of threat are sufficiently grave to legitimate actual bodily alterations affecting future generations. To put it somewhat differently, one might ask, "Of what kinds of good are parents properly the custodians?" How one answers has important implications for the judgment of what physical losses or limitations should call forth protection and intervention on the child's behalf.

## On Choosing Goods for Others

One effort to distinguish between detrimental and permissible exercises of parental power has contrasted acts and choices which have the effect of constraining or limiting the options or possibilities of the adult whom the child will become, with those which broaden those future options or leave them unaffected. In a religious liberty case which went to the Supreme Court, an Amish community sought protection for its right to keep girl children out of secondary school on the grounds that it rendered them less fit for their projected life and role within that community.[1] Part of the argument against protecting the Amish practice was that it severely constrained the later life possibilities of the women those girls grew into, and in effect constituted a barrier to any future decision to leave the community for a more "mainstream" form of life.

The case is interesting in that it concerns the limitations within which parents are permitted to choose a way of life, with particular forms of good and particular limitations, for their children. Hardly anyone contests the very broad latitude parents have in making such choices for their children while they are minors, or that these choices have some effects on the children's development and later life possibilities. For these reasons, asserting something like "a right to an open future"[2] may be an exaggeration of the degree of neutrality that is either possible or desirable in parenting. Religious communities in particular, by their nature, share a commitment to a particular account of goods at once fundamental and overarching, in light of which all others are to be judged. And such communities usually make serious attempts to nurture their children into the acceptance of these commitments, the embrace of these goods, and the adoption of the ways of life that embody them. These attempts may be pre-

sumed to have *some* kind of limiting effect, as indeed must any kind of socialization that is character-forming. Still, at some point the child's liberty to reject the community's beliefs and way of life is affirmed, and among Christians and Jews at least it is affirmed on substantive religious grounds. In the end, the religious good (the communion with God and neighbor) is and must be *constituted* partly by the adult's free embrace of the tradition and its commitments.

There is a different kind of concern about choices which have the effect of determining the forms of the good that may be embraced or pursued by the future adults, especially when they rule out other recognized and central goods those adults may come to desire. If these concerns arise regarding cultural practices like education, which are at least in theory reversible, they might be thought to apply much more strongly to genetic alterations, which are basic and irreversible. Clearly, intentional genetic modifications that can be safely introduced and that have the effect of correcting a disorder or preventing a disease have the effect of opening up the child's future, not of narrowing it. But changes that aim to confer particular traits, even traits that confer clear advantages in a given context, are more ambiguous. The assessment (positive or negative) of such things as height, appearance, and strength depends on a variable set of social valuations. It is not clear that the things prized by a given culture have the kind of moral standing which would justify our intervening to provide them for (or impose them upon) our children. Do we get to decide on an athlete? a basketball player or a sumo wrestler? or a musician? Who counts as a musician? Do we select for the talents of Yo-Yo Ma or Ray Charles?

Even traits with great flexibility (e.g., intelligence) presume a choice about the center of human value, satisfaction, and meaning. What is our standing vis-à-vis such binding choices of the good for the human which we might make and impose on our offspring? Does it belong to us as fellow creatures to make such choices forever, not at the level of background or upbringing or education, formative as these may be, but even at the level of being, the very character of cells? Can we do that not only for our own children, but for children in future generations as yet unthought of? Here perhaps is arbitrary and unjustifiable power, not to be exercised by one creature over another, even with the best intentions. I would argue that the goods we can justify choosing for each other in so decisive a fashion as inherited genetic intervention belong to the category of goods of the species, of the organism. They are the goods of the creature as given, not the goods of human culture, with all its variability, ambiguity, and corruption.

Eric Juengst in his article on enhancement makes in passing the assertion that "the personal improvement of ourselves or our children is morally laudable."[3] Not only does such an assertion beg the question of what constitutes improvement and how we decide, but also it is not beyond question even if we grant the goodness of a particular modification. The dispositions toward human existence that are fostered by the theological commitments of Jews and Christians include hospitality, generosity, humility, and trust. We are inclined to welcome the unknown, even the inconvenient and the less than desirable, because we ourselves are in many respects less than optimal or desirable and yet we need welcoming. We foster liberty in our growing children even to our own detriment as a mark of respect for our child's primary origin and ultimate belonging elsewhere. We are somewhat modest in our efforts to control the reality of the child because we do not necessarily believe that we have a complete picture of the good, or for that matter of evil. And, like the producer in *Shakespeare in Love,* we have a very deep though suitably chastened trust that "it will all work out," even though the time frame in which it works out may in fact extend beyond history; even though we acknowledge with him, "I don't know how; it's a mystery."

## The Usefulness of a Fuzzy Distinction

There is an ongoing and interesting debate over the conceptual fuzziness and contextual dependence of the distinction between therapy and enhancement. But the fact that a difference accrues gradually and is hard to pin down to a decisive shift does not mean there is no distinction between an acorn and an oak tree. The differences between a toddler and a twenty-five-year-old are substantial and they matter, even if it is not possible to propose a stable, universal, and reliable date for adulthood. Some arbitrariness is inevitable, and it is a matter of assessing cultural values and social context to determine on which side we ought to err in a given case. Still, if we are going to pursue any inheritable genetic modifications, we can and must make a distinction between medical therapy and elective enhancement, and form public policy accordingly. If there is some ambiguity about how short you have to be to be considered disabled and a candidate for therapeutic intervention, it is not impossible to identify the range of normal variation and draw lines around those who are within one or two standard deviations of the norm. Suppose it can be demonstrated that a particular body type, although not required for health, does nevertheless

confer a certain social advantage in a particular context. One may acknowledge that body type as a generally desirable trait without identifying it so closely with fundamental well-being that securing it justifies genetic intervention. For myself, I am basically happy with Eric Juengst's "disease-model" or his formulation that "enhancements are modifications aimed at normal and healthy traits,"[4] although he and others point out the limitations of that model. Other proposals that define enhancement in terms of the perversion of the goals of medicine or the morally "corrosive" circumvention of individual and social agency also may have something to offer our moral reflection and policy formation. What I would resist is the assumption that the absence of a perfectly formulated and impregnable distinction should lead us to the conclusion that no moral judgments in this realm can be justified. This will force us either to erect an in-principle prohibition which we cannot defend, or a completely permissive "consumer choice"–based practice which we should not defend.

## Recommendations

I am going to hazard a proposal about what this account of parenthood implies for the resort to germ-line intervention. First, the attitude of respect for the child grounded in religious awe should make us extremely cautious about the degree and kind of control we seek to exercise over its genetic characteristics. Seeking to select the genetic characteristics of our offspring in accord with cultural values or parental preferences is incompatible with honoring the dignity of a creature whose source and destiny is in God. Christians and Jews believe that the final and comprehensive good for the human being is given in that relationship rather than secured by any social or material giftedness or advantage. Therefore, genetic interventions aimed at increasing or enhancing positive characteristics, even real goods such as intelligence or creativity, cannot be defended as essential to well-being and should be forgone.

At the same time, the possibility of identifiable genetic errors that can create severe dysfunction, grave illness, and suffering as well as early death *do* seem to conflict with God's will for human flourishing in the same way as other serious disorders. Because of their developmental effects, some of these cannot be treated effectively in any other way than by germ-line intervention. If all the concerns for the reliability of correction, insertion, expression, and inheritance of genetic material can be addressed, and the safety of such limited changes in the gene pool assured to a level comparable with the known risks of leaving

such defects unaddressed, I see no absolute barrier to such interventions in the limits of human stewardship.

From the third moral characteristic of parenting, the attitude of unconditional acceptance, we might take one more lesson. It seems clear that, in a world where we have proven unable to provide every child with adequate nutrition, clean water, and basic immunizations, we are hardly going to rid the human family of genetic defects, even of the single-gene identified defects that are most amenable to correction. Nor are we ever going to become immune to other kinds of accident and mishap which bring into the world and into the human community children with various defects, disabilities, or challenges. Thus, we are never going to be finished with the need to accept and cherish and nurture children who are not as we might wish them to be, even for the purest of altruistic motives. For the sake of our capacity to fulfill the obligations of parenting, as well as the more basic obligation to emulate the grace and graciousness of God toward us, we cannot afford to neglect the attitudes, the practices, and the disciplines that equip us to embrace our children as they come to us, even as we have been embraced.

NOTES

1. *Wisconsin v. Yoder,* 406 U.S. 205 (1972).

2. This phrase is Joel Feinberg's in "The Child's Right to an Open Future," in *Whose Child?: Children's Rights, Parental Authority and State Power,* ed. William Aiken and Hugh LaFollette (Totawa, N.J.: Littlefield, Adams and Co., 1980), 124–53.

3. "What Does *Enhancement* Mean?" in *Enhancing Human Traits: Ethical and Social Implications,* ed. Erik Parens (Washington, D.C.: Georgetown University Press, 1998), 31.

4. Ibid., 32.

CHAPTER SIXTEEN

# Inheritable Genetic Modifications

## Do We Owe Them to Our Children?

Pilar N. Ossorio, Ph.D., J.D.

The notion that existing people possess obligations to their descendants is deeply ingrained in most societies. Many believe that one important measure of the character and quality of a person's life or a society's actions is the degree to which concerns for future generations are integrated into present decisions. Have we built up savings for our children and grandchildren? Is society leaving a world heavily polluted, or a world of clean water and accessible natural resources? Acting for the good of future generations is considered admirable, and perhaps ethically required.

The concept of obligations to future generations inevitably comes into play in any ethical assessment of inheritable genetic modification (IGM) of humans. IGM will affect the child who is born as a result, and could affect that child's entire lineage.[1] Should not our concerns for the health, safety, and best interests of those who will live in the future play a prominent role in determining whether IGM in general, or IGM in any particular instance, is ethically justifiable?

Commentators with differing and sometimes opposing views point to the effects of IGM on future generations to support their positions. Proponents of

IGM research claim that physicians' and society's obligations of beneficence toward those who will live in the future require research into IGM, and eventually the application of some IGM techniques. They contend that the medical profession has an obligation to use the best available technologies to prevent genetic pathology—an obligation that includes the use of IGM if or when this technology becomes available.[2] Some scholars have argued that, at least under some circumstances, parents have obligations to avoid giving birth to children whose disabilities have a genetic etiology.[3] Opponents of IGM point to its risks and dangers for offspring and their lineages, and claim that our obligations to future generations should preclude IGM research and application.[4] One commentator has argued that the interests of future children are not morally cognizable in many reproductive decisions;[5] however, other commentators claim that ethical analyses of assisted reproduction, including the potential use of IGM, are incomplete and "socially impotent" to the extent that these analyses focus solely on parents' reproductive liberties and ignore future children's interests.[6] Thus, existing scholarship suggests that parents, physicians, researchers, research funders, and regulators have ethical responsibilities to consider future people when making decisions regarding genetic interventions.

While the concept of obligations to future generations has broad intuitive appeal, one quickly confronts logical anomalies in applying it.[7] For instance, attempts to make reproductive decisions on behalf of a future child will often change who is born. In attempting to act on behalf of a future person we may cause that person not to exist and cause somebody else to be born instead. But how can we do something on somebody's behalf if she or he never exists? This problem is referred to as the "nonidentity problem."[8] For the remainder of this chapter I will argue that nonidentity could occur in the application of IGM, that nonidentity is relevant for assessing the ethics of IGM interventions, and that the ethical approach suggested by many as a means of evaluation in the face of nonidentity is problematic and perhaps unnecessary.

## Benefiting and Harming Future Persons

Personal and professional duties of beneficence are generally conceived of as duties to advance the interests of others and refrain from harming them. As noted above, arguments in favor of IGM include the claim that parents, physicians, researchers, and society owe it to future people to employ IGM to prevent or alleviate inheritable diseases. Some scholars have argued that parents

may, on occasion, be obligated to use IGM to enhance certain of their descendants' characteristics to provide them with at least an average opportunity to compete for basic goods.[9]

On the other hand, arguments against IGM include the claim that the risks of harm to future generations are too great. We harm others when we cause a net setback to their interests or a violation of their rights. Harming others is generally considered wrong, unless there is a justification or an excuse for doing so. Harm to others is the most widely accepted reason to limit the personal freedoms of citizens in a pluralistic, liberal society. Some would argue that it is the only reason to limit individual liberty,[10] such as the liberty to conduct research or pursue the procreative use of IGM. Thus, the question of whether and how one can harm one's future offspring through IGM becomes crucial.

But what does it mean to harm a future child? The philosopher Derek Parfit provides us with a demonstration of why traditional concepts of harming and benefiting may be incoherent when applied to future people.[11] Suppose that we are confronted with a fourteen-year-old girl who wants to have a child. Statistics tell us that a child born to a fourteen-year-old is likely to have a fairly bleak, impoverished life. Most people would counsel the young woman to wait until she is older, has a stable income, is more emotionally mature, and has a committed partner or some other stable social situation in which to raise her child. However, if she does wait to conceive, then the child to whom she gives birth will be a different person than the child she would have had when she was fourteen. Call the child she would have had at fourteen C1, and the child she would have at a later time C2. C1 will be a different child than C2 because when our young mother waits several years to conceive, a different egg will meet a different sperm, and the developmental conditions will be different.

If the young woman delays childbearing, can we say that her decision was better for "her child"? In the preceding sentence, the referent for the phrase "her child" is ambiguous. The young woman's decision to delay was not better for any particular child. If she delays, then C1, who probably would not have had a very good life, would not come into existence. Instead, C2 will come into existence. C2 will probably have a better life than C1 would have had. We cannot say, however, that C1 benefited because her or his mother delayed childbearing—C1 was never born.[12] And if the young woman had not delayed, had instead given birth to C1, then we probably could not say that C1 was harmed. C1's only other option would have been nonexistence, and so long as C1's life was better than nonexistence we could not say that C1's interests had been set

back by being caused to exist. This would be true even if C1's life were not a particularly happy one, and even if many life plans were unavailable to her. C2 has not benefited in the sense that her life is not better than it would have been if her mother had instead given birth at age fourteen. That child would have been C1, a different child.

The above story illustrates the nonidentity problem—when our decision changes who is born, then so long as whoever is born has a life worth living our usual conceptions do not allow us to say that anybody was harmed or benefited as a result of the choice we made.[13] This becomes problematic if we want to rest our assertions regarding the morally unacceptable or acceptable uses of IGM on claims about harms or benefits to future persons.

Note that the nonidentity problem does not arise because of epistemological indeterminacy, but because of lack of ontological identity. The problem is not that we do not know who will be harmed or benefited, it is that we change who will be born. Clearly, we can harm or benefit people we do not know. Engineers who design airplanes and bridges do not know the identities of people who will use these items. Nonetheless, anybody who flies in a plane or drives across a bridge will have interests in not being injured. If an engineer is reckless or negligent in designing a structure or vehicle, and somebody is injured as a result, then the engineer's actions harmed that person. That the engineer did not know who would be harmed is irrelevant.

Also, the nonidentity problem does not arise simply because persons who might be harmed or benefited do not yet exist (are not born and, perhaps, not yet conceived) when the relevant decision is made. People who will live in the future can be harmed by our present actions. Suppose I plant a bomb under the Empire State Building, set to explode five years from now. Suppose the bomb does explode in five years, injuring or killing numerous people, including several who are younger than five years old. My actions five years earlier can correctly be said to have harmed those people, including those who were not yet conceived or born when I planted the bomb. There is no logical inconsistency in holding that an act performed now causes harm if it eventuates in a bad effect on somebody in the future.

The difference between the bomb scenario and some reproductive choices that leads to the nonidentity problem is that my planting the bomb did not change who would be born. All and only the same children would have been born whether or not I had planted the bomb; the existence of any children who were injured or killed was not dependent on my planting the bomb. There is a

possible world in which those same children could have lived and not been injured by the bomb. The bomb heuristic indicates that our common understandings of harm and benefit can operate with regard to future persons so long as all and only the same people will be born regardless of the choice being made or evaluated. Unfortunately, many reproductive decisions, including (I contend) many decisions about the use of IGM, will change who is born and will, therefore, confront the nonidentity problem.

## A Brief Discussion of Genomes and Personal Identity

The nonidentity problem occurs because a decision changes who will be born. In some cases the claim that a different person will be born is fairly uncontroversial and will be widely accepted; in other cases, this claim will be far more ambiguous and controversial. Consider the fourteen-year-old girl scenario discussed above; one reason we say that C1 and C2 would, in fact, be different people is that they would have different genomes. We know that they would have different genomes, even if the egg and sperm came from the same woman and man, because of facts about biology. Women release one or a few eggs each month, and if these are not fertilized they are shed from the woman's body during menstruation. Likewise, men manufacture new sperm every few days. The mechanisms by which eggs and sperm are produced make the probabilities vanishingly small that any two eggs would be genetically identical or that any two sperm would be genetically identical. If a woman waits even one month to have a child, the egg that gives rise to that child's genome will be different than the egg that would have given rise to a child's genome a month earlier. In the fourteen-year-old's case, it is biologically impossible that two identical eggs would unite with two identical sperm several years apart, and thus C1 and C2 would have different genomes; their material of origin would not be numerically identical. Statistically, C1 and C2 would differ by approximately 50 percent of their genes (if they would have had the same parents), just as full siblings do. Under nearly all conceptions of personal identity, individuals who arise from different combinations of egg and sperm are, in fact, different people.[14]

However, from the fact of two different persons, we cannot infer two different genomes. Sometimes two different persons will result from a single fertilization event—for instance, when monozygotic (identical) twins are born. Monozygotic twins occur when one fertilized egg splits early in development.

Because monozygotic twins arise from a single fertilized egg, they have essentially identical genomes. We do not, however, think of monozygotic twins as being the same person. They may appear physically quite similar, but we recognize them as having distinct and distinguishable experiences, memories, and personal histories. We think of them as having different, unique personal identities despite the fact that they possess the same genome and developed from the same fertilized egg. This means that there is not a one-to-one correspondence between a genome or fertilized egg and any particular personal identity. Put another way, a single genome or fertilized egg can give rise to numerically more than one person.

If the same genome can give rise to more than one person, then this should be true even when twins are not born. We should not infer a one-to-one causal relationship between a genome and any particular person who developed with that genome. For instance, if we took an in vitro fertilized egg and implanted it in woman A at time T1 it might give rise to child X, but if we took that same fertilized egg and implanted it in woman A at time T2 (several years later) it might give rise to a different person, child Y. This is because at T2 the developing embryo and fetus would likely face different intrauterine conditions. And while our society is currently focused on the causal role of genes in shaping human physical and behavioral traits, we also know that development plays an enormous and sometimes dominant role in shaping traits.

As a dramatic example, imagine that at T1 woman A is an alcoholic and drinks constantly throughout the pregnancy. Under these conditions child X would likely be born with fetal alcohol syndrome. Child X might have behavioral difficulties and limited cognitive abilities, she might do poorly in school, have difficulties finding and holding a job, and have problems with interpersonal relationships. On the other hand, suppose that the woman refrains from implanting the embryo at T1, and that she completely stops drinking sometime between T1 and T2. She implants the embryo at T2. In this case, she would give birth to a child who has the same genome that child X would have had, but this child is not born with fetal alcohol syndrome. Call the child born at T2 child Y. Child Y does not have unusual behavioral problems and has average cognitive abilities. Her experiences and life history will be substantially different from those that child X would have had. Are child X and child Y two different people, or the same person with very different properties and characteristics?

The answer to this question will depend on one's view of the necessary and distinctive properties of persons. It is beyond the scope of this chapter to elab-

orate a theory of personal identity; however, I will argue that under many existing theories it is plausible to say that X and Y would be two different people even though they would have arisen from the same genome.

First, note that determining the identity of X and Y raises questions of bodily identity and personal identity. I take bodily identity to mean the necessary and distinctive attributes of a body, and the necessary and sufficient conditions for spatiotemporal continuity of a human body. Personal identity refers to those necessary and distinctive attributes of a person, and the necessary and sufficient conditions for the survival of a particular person over time.[15] Below, I argue that in the hypothetical described above the same embryo could be said to give rise to different bodies at T1 and T2. Furthermore, because of the strikingly different consciousness and experiences to be expected for a person with fetal alcohol syndrome and one without, the embryo can be said to give rise to two different persons, regardless of whether it gave rise to two different bodies.

For those theories of personhood in which bodily identity is a necessary and distinctive criterion for human personhood, the question of whether or not X and Y would be two different persons will rest on whether or not the different intrauterine conditions led to changes in properties or attributes necessary and distinctive for bodily identity. If the necessary and distinctive attributes required include particular aspects of appearance, biochemistry, or brain physiology, then, arguably, X and Y would have different bodies. X's body, with fetal alcohol syndrome, would be measurably different in some or all of these characteristics than Y's body without fetal alcohol syndrome.

For those who hold that personhood and personal identity comprise something different than or in addition to bodily identity, it is easier to make the case that X and Y would have been different persons. Such theorists could hold that X and Y could have been born with the same body, but that the properties of the body when X was born into it ($body^X$) would have been relevantly different from the properties of the body when Y was born into it ($body^Y$), such that different persons would have developed in the body (rather than the same person with radically different properties).

For theories of personal identity in which personhood is more or different than bodily identity, necessary attributes for personal identity consist of such features as experiences linked to memories by a particular relationship (usually a causal one); intentions and attitudes linked to actions by a particular relationship; and other types of psychological continuity and connection. One could reasonably suppose that, from birth or before, the experiences to be had

by the person who would have been born with fetal alcohol syndrome in body$^X$ would be quite different from the experiences to be had by the person who would have been born without fetal alcohol syndrome in body$^Y$. X and Y would probably have qualitatively different perceptions and consciousnesses, and therefore, even if they could have been subjected to exactly the same sequence of events their experiences probably would have been different. X and Y would likely have very different capacities to formulate intentions and act on them, or to formulate memories. For these reasons, it is plausible to describe X and Y as different people who could have been born from the same fertilized egg.

Thus far I have claimed that (1) genomes that differ by as much as 50 percent necessarily give rise to two different people; and (2) one genome can give rise to numerically more than one person under some circumstances. But what happens if a genome is changed by one base pair? Some IGM methods might change only one or a few DNA bases ("gene repair," for instance); they would replace one allele with a different allele. Would these small interventions change who is born?

## The Nonidentity Problem and Inheritable Genetic Modifications

Most commentators have assumed that IGM would not change who is born. For this reason, some consider IGM morally different from other uses of genetics and reproductive technologies because they conceive of IGM as a technology for improving (or harming) the lives of particular future persons, rather than a means for selecting among different future persons.[16] But, if IGM does change who is born, then the nonidentity problem applies and IGM is not morally different on the grounds that it will improve (or harm) the lives of particular persons.

Genetic and reproductive technologies that have been identified as alternatives to IGM are generally agreed to change who will be born. One such technology is prenatal genetic diagnosis (PGD) and selective implantation (SI). In PGD & SI, embryos are created in vitro and subjected to genetic testing to exclude those with undesired alleles (embryos that are homozygous for Tay-Sachs or cystic fibrosis [CF] alleles[17] would be excluded, for instance). Embryos that pass the genetic screen, and that appear otherwise robust, are chosen for implantation.

PGD & SI provides a means of selecting among different future persons be-

cause the embryos subjected to this technology have different genomes. By choosing one embryo over another for implantation, one is substituting one person-who-will-be-born (or set of potential future persons who could develop from a particular embryo) for another. The nonidentity problem would apply if we attempted to describe PGD & SI as harming or benefiting somebody.

PGD & SI involves preventing a disease by preventing the birth of a person with the disease.[18] Most disease prevention involves preventing people from developing or catching diseases, a social practice reflecting our caring and beneficent moral norms. Preventing a disease by precluding people from being born with the disease less clearly reflects these norms precisely because of the nonidentity problem—if one prevents a person from being born with the disease then there is nobody we can point to and say, "Her life was made better by our actions." The first form of prevention represents a commitment to make somebody's life better; the second represents a commitment to make somebody who we believe (rightly or wrongly) will have a better life. The second form of prevention resonates with the eugenic notion of creating a "better" populace by preventing the births of people with disfavored genetics or encouraging the birth of people with favored genetics. Nonetheless, the desire to prevent genuine human pain and suffering is also embodied in the second form of prevention.

Compare the uses of PGD & SI and IGM to "prevent" the same disease. Suppose that each method were used to prevent CF. In the case of PGD & SI this would mean conducting genetic tests on embryos and excluding from implantation any that were homozygous (or perhaps even heterozygous) for CF alleles. If IGM were used, an embryo that was homozygous for a CF allele would be transformed into one that was heterozygous, and therefore the person born would not develop CF. Does this count as treating a particular person, advancing her interests, or improving her life? In my view, the answer is ambiguous. People living with CF have claimed that a person born from their embryo, but without CF, would have been a different person.[19] However, one could plausibly claim that IGM would have resulted in the same person being born, but with a different life history that did not include CF.

Now, consider the case in which IGM could be used to treat Lesch-Nyhan syndrome or Tay-Sachs disease. Lesch-Nyhan syndrome affects the central nervous system, resulting in spastic and uncontrolled movements, mental retardation, and compulsive self-mutilation.[20] Tay-Sachs affects neurological and

muscular development and is usually visible within the first six months of life. Symptoms include lethargy, floppiness, and difficulty feeding. The infant deteriorates, with deafness, visual impairment, and spasticity proceeding to rigidity. Death usually occurs by age three due to respiratory infection.[21] Both diseases are caused by known mutations; both affect fetal development and manifest in infancy. These diseases are more likely candidates for IGM than CF, because the biological problems resulting from Tay-Sachs- and Lesch-Nyhan-causing mutations may be irreversible by the time a child is born. Both diseases have global effects and lead to early death. Somatic cell genetic interventions on people already born probably would not succeed in curing or substantially ameliorating the effects of these diseases.

Suppose scientists and physicians could carry out gene repair, and change a single nucleotide in an embryo's genome from one that would have resulted in Lesch-Nyhan syndrome to one that would not. The embryo's genome would be essentially the same, and yet I contend that a different person would be born from that embryo. The person who would be born would probably have an IQ within the normal range, would not have uncontrollable spasticity, would not compulsively self-mutilate, and would have a life expectancy not limited by Lesch-Nyhan syndrome. At the earliest stages of self-consciousness her experiences of herself and the world would be substantially different than those of somebody born with Lesch-Nyhan syndrome. The manner in which she would think, feel, and interact with the world would be quite different.

Under many theories, the single nucleotide change just described would alter the entity in properties that are necessary and distinctive for personal identity. This means that IGM for Lesch-Nyhan syndrome, Tay-Sachs, and other relevantly similar diseases or conditions would constitute a means of replacing one person with another; IGM is a technique that may change who is born.[22] IGM in the Lesch-Nyhan case is not relevantly different from PGD & SI with respect to the nonidentity problem—if the parents and professionals chose to use IGM to prevent Lesch-Nyhan, it could not be said that they had benefited anybody.

On the other hand, imagine the use of IGM to change a genome such that it no longer contained or expressed a Huntington's disease allele. Huntington's disease is a neurodegenerative disease in which symptoms generally do not manifest until a person's late forties or fifties. It does not obviously affect fetal development or a person's youth. There is no reason to believe that IGM to change a Huntington's allele would alter the experience or behavior of the in-

fant who was born. There is no reason to believe that when she attained consciousness her experience of herself or the world would be different based on whether or not the embryo from which she developed had undergone IGM for Huntington's disease. In this case, one could reasonably argue that IGM improved a particular person's life. One could plausibly claim that one person's life history would be altered by IGM such that the person lived a life without Huntington's disease rather than a life with the disease. Here, IGM would not confront the nonidentity problem and it would be different, in morally relevant ways, from PGD & SI.

I have argued that there are cases in which IGM will not change who is born, cases where the effect of IGM on identity is ambiguous, and cases in which it will change who is born. Thus, some uses of IGM are distinguishable from uses of other reproductive technologies with respect to nonidentity and some are not.

Note that while there are many reproductive decisions that confront the nonidentity problem and therefore cannot be evaluated based on benefit or harm *to the future child,* there are other, common moral criteria for evaluating these decisions. The future child is not the only person whose life will be affected by the reproductive choice. Other members of the family and the community will be affected, and the moral evaluation of a reproductive decision must take these effects into account.[23]

## Person-Affecting versus Impersonal Principles?

Intuitively, many people feel that moral evaluation of reproductive decisions is not complete or sufficient if it does not account for the future child's interests and quality of life. And people feel that our reproductive ethics should aim toward reducing the amount of suffering in the world. Many believe that parents commit a wrong by giving birth to a child who will likely experience greater than average suffering, or who will have fewer than average opportunities and life plans, if those parents could instead give birth to a child who is likely to experience less suffering and have available a wider, richer variety of opportunities and life plans.[24] Some argue that when nonidentity occurs it should not influence our moral evaluation, that we should consider it wrong for parents to give birth to a disabled child when they could have given birth to a nondisabled child, even if no future child was harmed or benefited.[25]

Scholars who accept that nonidentity poses difficulties for harm/benefit-

based moral evaluation of many reproductive decisions have sought some other approach by which to judge these decisions. If applying standard notions of harm and benefit leads to counterintuitive results, then what other criteria can we use to account for future children in our moral calculus? To circumvent the nonidentity problem, Derek Parfit proposed the following principle: "If in either of two possible outcomes the same number of people would ever live, it would be worse if those who live are worse off, or have a lower quality of life, than those who would have lived."[26] Applying this principle involves comparing two possible future worlds and determining which one is better according to some scale of value. This principle is an example of impersonalism, and can be contrasted to more common, person-affecting principles or analyses. The contrast has to do with how we understand value to arise in the world.[27]

Impersonal theories ascribe value to states of affairs independently of effects on subjects. Using impersonal approaches we compare possible states of affairs, and although a state of affairs may be bad for people, this is not the reason why it is bad. When we apply person-affecting principles to future-generations problems, the object is to promote value in people's lives; when we apply impersonal principles, the object is to create new people whose lives manifest our values.

The nonidentity problem arises only in a world of person-affecting value. A person-affecting theory holds that goodness must always be "good for" or "good to" somebody. Goodness and badness depend on valuers for their existence; this is a claim about the ontology of value. A strong version of person-affecting value holds that for something to be good or bad for person A, it must be good or bad from person A's point of view.

There are many situations in which impersonal theories or principles and person-affecting ones would reach the same results. This will generally be true when the moral dictum is applied to contemporaneously existing people. For instance, if we speak impersonally of improving health, we generally mean that people's health should be improved. In this case, person-affecting and impersonal formulations would achieve the same result. Likewise, in future-generations problems, if all and only the same people would exist regardless of the choice made, then both approaches would allow for the possibility of obligations to particular individuals who will live in the future (recall the hypothetical discussed above in which I plant a bomb that explodes five years later). Impersonal principles may have broader reach, however, because they are intended to function in just those situations in which person-affecting ap-

proaches become incoherent due to the nonidentity problem; they were devised to provide moral guidance when our actions or choices cannot be said to affect particular people.

Parfit argues that we should employ impersonal principles because nonidentity is not morally relevant.[28] To illustrate this claim he proposes the following hypothetical:[29] imagine two medical programs, each of which screens for a problem that leads to the birth of children with disability D. One program screens pregnant women for an infectious disease that can affect their fetuses and cause their children to be born with disability D. If this prenatal screening detects the infectious disease, the woman can undergo a simple treatment, with no side effects, which cures the fetus and prevents her future child from being born with disability D. The other program screens women who are considering pregnancy for a condition that will cause them to conceive children who will later be born with disability D. If this preconception screening detects the condition, the woman can avoid giving birth to a child with disability D if she simply waits two months before getting pregnant. Although these programs screen for two different diseases, the disabilities detected and avoided will be identical; we stipulate that the degree of discomfort or inconvenience to the woman would also be identical. It is estimated that each program would lead to a thousand fewer children being born with disability D. Unfortunately, the society has only enough money to implement one of the two programs. Does it matter which one?

In the above hypothetical, prenatal screening is supposed to avoid the nonidentity problem; a person-affecting harm principle could apply. Preconception screening would clearly confront the nonidentity problem. If the woman waits two months to conceive, then a different sperm will unite with a different egg and a different child will be born without disability D than the child who would have been born if she had not waited. A person-affecting harm principle could not be applied to preconception screening; children born with disability D could not claim to have been harmed and children born without could not claim to have benefited. If your intuition does not distinguish between the prenatal screening and the preconception screening programs, then nonidentity may not be morally relevant for you.

Parfit's hypothetical may be misleading, however, because prenatal screening could also involve the nonidentity problem. Prenatal screening and treatment in the hypothetical could change who would be born in the same manner that IGM for Lesch-Nyhan or Tay-Sachs could change who would be born.

When confronted with Parfit's hypothetical many people will assume that the disability would be severe and life-changing. Why would society expend resources screening for something trivial? Furthermore, there still exists enough ignorance, fear, and prejudice about disability that people tend to conceive of disabilities in general as serious and substantially life-altering. I believe that these psychological facts will be true of most readers and will impel them to imagine that treating disability D in the fetus will lead to such substantial changes that a different person will be born. Thus, I do not think the hypothetical adequately distinguishes between a program that would confront the nonidentity problem and one that would not; it does not adequately distinguish between a situation in which person-affecting principles could legitimately be applied and a situation in which they could not.

Constructing a hypothetical to test moral intuitions regarding the importance of nonidentity is quite difficult. For instance, consider two cases of IGM for the hypothetical BEANS gene. Some alleles of BEANS cause a person to be born with significant cognitive impairments. These early-onset alleles have no negative health effects, and people born with early-onset BEANS live healthily and happily, but need substantial assistance to carry out daily activities. Other alleles of BEANS are late-onset alleles, which do not have any negative effects until the person is in her twenties. If a person has the late-onset allele, she will be born with ordinary cognitive abilities, but sometime in her twenties or early thirties she will quickly lose her cognitive abilities and become like the person who has early-onset BEANS. Arguably, in the case of early onset BEANS the nonidentity problem applies, and in the case of late-onset BEANS the nonidentity problem does not apply.

Suppose that society has only enough resources to conduct IGM for early-onset BEANS or late-onset BEANS, but not both. Further, suppose that each type of BEANS results in the same number of people becoming disabled in a given year. Does our moral intuition give us clear guidance about choosing one over the other?

If our moral intuition does not give us clear guidance, there could be several reasons. One is that it may be difficult for some to apply nonidentity to IGM for early-onset BEANS. Even if we can provide strong, logical arguments for the claim that more than one person can arise from a single embryo, this claim is still counterintuitive and our moral intuitions might address treatment for early-onset BEANS as treatment for a particular person. Our moral intuitions might be confused.

Another problem is that IGM for late-onset BEANS introduces an additional, morally significant feature into the scenario—the person who develops late-onset BEANS will be diminished, and will likely know that she is being diminished, at least briefly, while she loses her cognitive capacities. This is a significant harm, and one that may inspire a high degree of empathy from readers who could envision themselves losing capacities. Thus, early- and late-onset BEANS are not sufficiently symmetrical to test our intuitions about nonidentity.

This attempt to create useful cases is instructive, however, precisely because it highlights the fact that persons have complex sets of interests that are not easily disentangled or collapsed. One normatively important feature of person-affecting ethical approaches is that they focus our attention on the needs, interests, experiences, and life histories of others. The other-regarding nature of person-affecting principles requires us to pay attention to the details of lives different from our own. When compared to impersonal principles, person-affecting principles provide a sounder basis for separating those moral prohibitions or mandates that are grounded in concern for human welfare from those grounded merely or primarily in prejudice or ideology. Given that the medical uses of IGM (and other reproductive technologies) would be directed toward preventing disabilities, and that ignorance and prejudice concerning disabilities abound, we should be concerned about the degree to which our ethical approaches may be contaminated by prejudice or naive and unwarranted assumptions.

Reproductive ethics may be characterized by the need for some impersonal principles; however, I do not think that we should easily accede to the notion that wrongs as defined by impersonal principles are as bad as person-affecting harms. To equate injuring one's child with adding to the world a person who has an overall decent life but who also has a disability seems to either demonize disability or diminish the seriousness of harming one's child.

In addition, the impersonal principles thus far proposed for evaluating reproductive decisions confront epistemological problems that may be insurmountable. Consider the situation of a woman attempting to apply Parfit's principle after a genetic test result indicates that her fetus is homozygous for a CF mutation. Recall that the principle states, "if in either of two possible outcomes the same number of people would ever live, it would be worse if those who live are worse off, or have a lower quality of life, than those who would have lived."[30] How can the pregnant woman apply this principle to help her reach a justifiable conclusion?

Our prospective mother is supposed to compare two possible outcomes in which the same number of people would ever live. Let us assume that she can achieve this by imagining that if she does not give birth to this child she will become pregnant again and give birth to some other child, so she is comparing two possible future worlds in which she adds one child. She cannot predict the severity of the illness in the child who would result from the genetically tested fetus. This future child's CF may range from reproductive impairment but no other significant health effects, to serious pancreatic insufficiency, lung infections, and early death. She does not know whether the person who would be born if this fetus develops would have musical or athletic genius, would be an optimistic person, would get engaged to somebody who died before the marriage, or would become the president. She knows nothing at all about a different future child who might come into being if she attempts another pregnancy.

To apply Parfit's principle, the woman must compare quality of life for people who will live in alternative future worlds; the relevant people would be the two, alternative future children, and existing family members (at least). No methodology exists for undertaking this comparison. Philosophers and economists have yet to devise a widely accepted method for determining the quality of life of existing people at a given point in time, much less summed across entire life spans. Our reproductive decision maker would have to play forward two hypothetical worlds for some indefinite period of time and compare the quality of life in each, for all of the relevant people, on the basis of only one piece of information—the presence of CF alleles in the currently existing fetus. This seems an impossible task, and one that would likely collapse into a meditation on the difficulties that might face a person who would live with CF, or the difficulties that might face her family.

What little data we have indicate that many people with disabilities do not rate their quality of life any lower than people without disabilities.[31] Data on the effects of a child with a disability on other family members are equivocal.[32] Thus, if our decision maker was attempting to use empirical information she would find that the one piece of information she has about the two future worlds—that one would contain a new person with CF—is not particularly helpful in determining whether her choice to continue the pregnancy is a good one. I suspect that this would be true for all but the most severe of genetically detectable disabilities, such as those that cause significant pain and early childhood death.

If impersonal principles can only produce clear guidance in the most extreme cases then we may not need them after all. The standard person-affecting harm principle might yield approximately the same results, because disabilities that are so severe as to cause a painful, early death might be exactly those judged to create a life worse than nonexistence. Birth with those most severe disabilities could reasonably be considered a harm to the person who is born. In addition, the birth of a child with a disability that leads to a painful, early death would more likely have clear, net negative effects on other family and community members whose interests must also be considered under a person-affecting analysis.

## Conclusion

IGM is generally thought of as a technology or set of technologies that would be used to treat or enhance a person. In some respects, it may be perceived as morally superior to other forms of assisted reproduction because it is regarded as an attempt to improve the life of a particular person. Other forms of assisted reproduction, such as prenatal genetic diagnosis and selective implantation, are more easily recognized means by which a future person who would have been born with a particular disability could be "replaced" by a person who would not be born with that disability. Therapeutic IGM is seen as preventing a disease from developing in a person, while other forms of assisted reproduction involve preventing the occurrence of a person who would develop a disease.

I have argued that there will be many cases in which IGM would also constitute a form of replacement. Changing even one gene or one nucleotide could so significantly alter a person's experiences, opportunities, life plans, and interactions with the world, from the beginning of her life, that the result of IGM would be the birth of a different person. Thus, ethical assessment of IGM may also be plagued by the nonidentity problem. For those cases in which IGM changes who will be born, we cannot say that we owe it to any future child to use IGM or not.

Numerous commentators have suggested that we need a radically new ethical approach for making moral judgments when confronted with the nonidentity problem. This new ethical approach would employ impersonal principles of some sort. While it may be the case that reproductive ethics will include some impersonal principles, I argue that the impersonal principles sug-

gested thus far are impractical and doomed to ineffectiveness by epistemological and methodological uncertainty.

NOTES

1. Whether an entire lineage will in fact be affected depends on whether the person born as a result of IGM lives to reproductive age, whether she or he chooses to reproduce, and whether future members of the lineage choose to reproduce. In addition, the longevity of an inheritable genetic modification might depend on whether further modifications occur in that lineage to reverse or alter the initial genetic intervention. It is not necessarily the case that any inheritable genetic modification will be with the human race indefinitely.

2. See Burke K. Zimmerman, "Human Germ-line Therapy: The Case for Its Development and Use," *Journal of Medicine and Philosophy* 16 (1991): 593–612; Nelson Wivel and LeRoy Walters, "Germ-line Gene Modification and Disease Prevention: Some Medical and Ethical Perspectives," *Science* 262 (1993): 533–37.

3. Dan Brock, "The Non-Identity Problem and Genetic Harms: The Case of Wrongful Handicaps," *Bioethics* 9 (1995): 269–75; Ronald Green, "Parental Autonomy and the Obligation Not to Harm One's Child Genetically," *Journal of Law, Medicine and Ethics* 25 (1997): 5–15.

4. Paul Billings, Ruth Hubbard, and Stuart Newman, "Human Germline Gene Modification: A Dissent," *Lancet* 353 (1999): 1873–75.

5. David Heyd, *Genethics: Moral Issues in the Creation of People* (Berkeley: University of California Press, 1992).

6. Glenn McGee and Ian Wilmut, "Cloning and the Adoption Model," in *The Human Cloning Debate,* ed. Glenn McGee (Berkeley Hills Books, 1998).

7. For a thoughtful discussion of the logical problems in considering obligations to future generations, see Heyd, *Genethics: Moral Issues in the Creation of People,* chaps. 1–3.

8. Derek Parfit, *Reasons and Persons* (New York: Oxford University Press, 1984), chap. 16.

9. Allen Buchanan, Dan W. Brock, Norman Daniels, and Daniel Wikler, *From Chance to Choice: Genetics and Justice* (Cambridge: Cambridge University Press, 2000), chap. 5.

10. John Stuart Mill, *On Liberty and Other Essays* (Oxford: Oxford University Press, 1991), 14.

11. Parfit, *Reasons and Persons,* chap. 16.

12. C1 cannot have benefited by never having been born because there would be no subject to experience this "benefit." Even if we think that, had C1 been born, her life would have been worse than nonexistence, and therefore a harm to her, we cannot say that C1's not being born is a benefit *to her.*

13. I am assuming that being born is not, itself, a benefit. Scholars disagree on this point. However, if being born with a life worth living is a benefit, then it does not re-

ally distinguish between C1 and C2; either one would have received this benefit from us and the one who is not born is not harmed by not being born.

14. Parfit discusses some views of personhood under which it could be claimed that a person might have originated from a different sperm and egg than that from which she or he did originate. For instance, holders of various "Descriptive Views" of personal identity might claim that my necessary and distinctive properties consist merely in my being my parents' first child. As Parfit notes, this view leads to the absurd conclusion that, had my parents not given birth to me, then my younger brother would have been me (because he would have been my parents' first child). Most such views are counter-intuitive and face many objections. Parfit, *Reasons and Persons,* 351–55.

15. Many theories of personal identity take it as possible that personal identity is separable from bodily identity. See, for example, John Locke, "Of Identity and Diversity," in *Personal Identity,* ed. John Perry (Berkeley: University of California Press, 1975), 33–52; Sydney Shoemaker, *Self-Knowledge and Self-Identity* (Ithaca: Cornell University Press, 1963), 22; and Parfit, *Reasons and Persons,* part 3. For this reason, theorists frequently seek to elucidate the criteria for personhood through thought experiments involving brain transplants, memory transplants, teleportation, or other hypothetical situations in which a person might survive separated from a particular body. On most accounts, personal identity is related to mind, and recent scholarship on the nature of mind and consciousness has called into question the possibility that mind and body can, in fact, be separated. However, even conceding that mind and body are not separable, we need not rule out the possibility that more than one mind or one person could develop in a particular body.

16. Of course, the argument cuts both ways. Opponents could also view IGM as worse than alternatives such as prenatal diagnosis and selective abortion (PGD & SA) on the theory that IGM could harm particular persons whereas the alternatives merely substitute one potential person for another and do not harm whoever is born as a result of using the technology.

17. Cystic fibrosis and Tay-Sachs are recessive conditions, so disease-causing mutations must be found in the genes inherited from both the mother and the father for the disease to develop in a child. If a child is born with the disease, it means that the parents were each carriers. A carrier for a recessive condition has one allele that would cause the condition and one allele that would not; therefore, she or he will not have the disease. Whenever two carriers have a child together, there is a one in four chance that the child will be born with the disease.

18. Eric Juengst, "'Prevention' and the Goals of Genetic Medicine," *Human Gene Therapy* 6 (1995): 1595–1605.

19. Suzanne Tomlinson, "Genetic Testing for Cystic Fibrosis: A Personal Perspective," *Harvard Journal of Law and Technology* 11 (1998): 551–63.

20. Robert Mueller and Ian Young, *Emery's Elements of Medical Genetics,* 9th ed. (Edinburgh: Churchill Livingtone, 1995), 138.

21. Ibid., 137.

22. Robert Elliot, "Identity and the Ethics of Gene Therapy," *Bioethics* 7 (1993): 27–40; Ingmar Persson, "Genetic Therapy, Identity and the Person-Regarding Reasons," *Bioethics* 9 (1995): 16–31; Robert Elliot, "Genetic Therapy, Person-Regarding Reasons and the Determination of Identity," *Bioethics* 11 (1997) 151–69.

23. Heyd, *Genethics: Moral Issues in the Creation of People,* chap. 7.

24. Buchanan, Brock, Daniels, and Wikler, *From Chance to Choice: Genetics and Justice,* chap. 5; Philip Peters, "Protecting the Unconceived: Nonexistence, Avoidability, and Reproductive Technology," *Arizona Law Review* 31 (1989): 487–58; Ronald Green, "Parental Autonomy and the Obligation Not to Harm One's Children Genetically," *Journal of Law, Medicine and Ethics* 25 (1997): 5–15.

25. Parfit, *Reasons and Persons,* 366–71.

26. Ibid., 360.

27. Heyd, *Genethics: Moral Issues in the Creation of People,* chap. 3.

28. Parfit, *Reasons and Persons,* 360.

29. Ibid., 367.

30. Ibid., 360.

31. Erik Parens and Adrienne Asch, "The Disability Rights Critique of Prenatal Genetic Testing: Reflections and Recommendations," in *Prenatal Testing and Disability Rights,* ed. Erik Parens and Adrienne Asch (Washington, D.C.: Georgetown University Press, 2000).

32. Philip Ferguson, Alan Gartner, and Dorothy Lipsky, "The Experience of Disability in Families: A Synthesis of Research and Parent Narratives," in *Prenatal Testing and Disability Rights,* ed. Parens and Asch.

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CHAPTER SEVENTEEN

# National Policies to Oversee Inheritable Genetic Modifications Research

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This chapter presents recommendations for regulating research related to inheritable genetic modifications (IGM). In producing these recommendations, we analyzed current limits that have the potential to apply to IGM, including rules promulgated by the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH), federal human subject protections, Food and Drug Administration (FDA) regulations that apply to somatic cell gene transfer trials, and state laws that might apply to IGM. Our analysis includes comparisons with historical approaches to somatic cell gene transfer and the flaws in those approaches. Several of our recommendations, in fact, are derived from flaws in previous regulatory models that should be remedied in establishing a review mechanism for IGM. Our work on these recommendations benefited from and was informed by our participation in the AAAS working group process.

## Recommendations

Our proposed regulatory approach includes the following characteristics:

1. A national standing body should prospectively review IGM research proposals, based on considerations similar to those used by the RAC in reviewing somatic cell gene transfer protocols. These considerations include alternative treatments, potential harms and benefits, fairness in the selection of research subjects, informed consent, and privacy and confidentiality. The IGM review process should consider new issues as well, such as impact on future generations and potential social harms and benefits.
2. Review of IGM research proposals should be public and should include opportunities for public comment.
3. Jurisdiction should extend to privately funded research as well as to research in institutions that receive federal funds.
4. Regulatory review should be triggered by substantive ethical issues (such as risk to research participants and implications for society) rather than by the type of technology employed to accomplish the IGM.
5. Violations of the review process should be referred to the Office of the Inspector General or another organization independent of those funding and conducting the research, which has the ability to carry out a credible investigation. Alternatively, the standing body should have the capacity to investigate violations of the review process. Sanctions for violation should be sufficient to create strong incentives for compliance.
6. The regulatory mechanism should include a clear process for reporting adverse events associated with research.
7. The standing review body should be based in a part of the government where it would not suffer from conflicts of interest engendered by its administrative home having a dual capacity as an IGM-funding agency.
8. The standing body should be multidisciplinary, represent diverse interests, and include nationally respected members of the "IGM community."
9. The national review of IGM research proposals should follow local institutional review board (IRB) review chronologically. This federally prescribed two-part review process should preempt state and local rules regarding IGM research.

## Explaining Our Recommendations

### *Prospective Public Review*

We recommend prospective review of IGM studies that pose risks for participants or for other reasons raise ethical and legal questions. Criteria for approving human studies must be specified and a body should be constituted to perform the review of study protocols according to these criteria. We believe prospective approval of studies that propose to cause inheritable genetic modification will be needed to address religious and ethical concerns and also to ensure that studies are safe and likely to yield valuable scientific information to improve future therapies. The closest model for this type of prospective review of gene therapy can be found in the history of somatic cell gene transfer oversight by the RAC.[1] The RAC lost its authority to approve gene transfer proposals, except in certain narrow circumstances, in 1995. We use as our model the RAC as it was before it lost this authority.

The U.S. Food and Drug Administration (FDA) also reviews somatic cell gene transfer proposals. The FDA review is conducted confidentially, however. For IGM research, there is a strong need for open public disclosure and public input. The FDA process protects the proprietary interests of firms and investigators, but at the cost of submerging debate beneath the surface, dramatically reducing the level of public scrutiny. An open process does entail added costs and delay, and it creates points of intervention for those who wish to impede research. For example, the first gene transfer protocol was delayed for several months by a lawsuit filed to block it.[2] Nevertheless, in our view, this procedural cost is more than balanced by the enhanced credibility and public accountability of the open review process. Moreover, an open process also ensures multiple entry points for public participation and recurrent opportunities for media coverage. The first somatic cell gene transfer protocols were well known to the public in large part because of the RAC review process. Press accounts attended each step in the process, in contrast to the parallel FDA process that engendered almost no publicity and few opportunities for public comment. Our proposed model does not require FDA to renounce IGM review. Rather, responsibilities for review could be shared by the mechanism we propose and by the FDA. Dual review by the FDA and the proposed (RAC-like) IGM regulatory body would ensure a public process as well as the type of technical review that the FDA has a long history of doing well. Alternatively,

the FDA's responsibilities for review could be reassigned to the new regulatory mechanism.

### *Jurisdiction*

The IGM regulatory mechanism should have jurisdiction over both privately and publicly funded research. Even before the removal of the RAC's approval authority, the RAC did not have jurisdiction over research in privately funded institutions. Its jurisdiction extended only to research in institutions that received federal recombinant DNA research funds. The sanction for violations of the guidelines was loss of an institution's recombinant DNA funds. A better system of oversight would encompass all affected individuals and groups so that no unacceptable IGM experiments would slip through the cracks.

### *Substantive Criteria*

The review of IGM proposals should be triggered by criteria that emphasize risk to prospective participants and ethical concerns, not the particular technologies employed. RAC's review process is triggered by whether recombinant DNA is involved in a study, a technological feature irrelevant to our concerns with IGM. It is not the nature of the technology but rather the risks and ethical concerns that should determine the need for review. The scope of review should be specified by the IGM oversight body in consultation with NIH, FDA, other agencies in the Public Health Service, Congress, religious groups, centers of bioethics, professional and scientific societies such as the American Fertility Society, the American College of Obstetrics and Gynecology, the American Society for Human Genetics, and patient groups such as the Genetic Alliance and other similar organizations.

### *Referral to the Office of the Inspector General*

We recommend that alleged violations of the regulatory process should be referred to the Office of the Inspector General (OIG), Department of Health and Human Services. Previous NIH investigations of alleged scientific misconduct, infractions of recombinant DNA guidelines, and violations of human subject regulations have lacked credibility; credible investigations require attention to due process and staffing and are best left to organizations with such capacity. The RAC investigation of violations at the University of California, San Francisco, in 1977, for example, revealed weaknesses in this area.[3] The vio-

lations involved use of an uncertified vector to clone insulin and growth hormone at the University of California, San Francisco (UCSF).[4] What actually transpired remains uncertain more than two decades later,[5] and what is known derives far more from a patent case in federal court[6] than from NIH's "investigation." Similarly, NIH's handling of scientific misconduct cases, and specifically its inattention to due process, has been vigorously criticized, most notably in a recent history of its most prominent case, a ten-year investigation concerning Thereza Imanishi-Kari.[7] Finally, a series of reports from the Office of the Inspector General, Department of Health and Human Services, notes limits on the powers of the Office of Protection from Research Risk (OPRR), also part of NIH, when questions arise about transgressions of federal human subject protections.[8] (The OPRR was recently reconstituted outside of NIH as the Office for Human Research Protections.) This recurrent problem in disparate parts of NIH has not led to the most logical remedy, a process for referring cases that cross a threshold for investigation to the OIG, Department of Health and Human Services, or some other credible authority with the requisite capacity and competence.

### *Reporting Adverse Events*

Any regulatory mechanism governing IGM research should include a well-delineated process for reporting adverse events associated with the research. The lack of clear reporting rules has plagued the RAC and the FDA in recent years, and alleged violations of the reporting process have been highlighted by the Jesse Gelsinger case. The NIH and FDA reviews following Gelsinger's death revealed that "many researchers were not immediately reporting serious patient complications, including deaths."[9] Some researchers have asserted that reporting is not required when the therapies in question do not appear to be responsible for the adverse events. Others have suggested that the differing reporting requirements of NIH and FDA make it difficult to determine the standards for reporting. The FDA and the RAC have recently begun to consider alternative reporting requirements, methods of enforcing reporting requirements, and ways to force better monitoring of patient safety.[10] Lack of clear reporting requirements and a mechanism to enforce reporting of adverse events have made noncompliance with reporting requirements a problem in the current system.

One of the key problems with establishing reporting requirements in somatic cell gene transfer research has been the tension between confidentiality

claims due to commercial concerns and patient privacy issues on one hand, and the need to promote open discussion of the issues on the other hand. The same issues will arise in relation to IGM research. The reporting requirements built into the IGM regulatory mechanism must address this tension. The current review of reporting requirements following the Gelsinger case should prove instructive.

### *Conflict of Interest*

One of the flaws in the RAC model of review is the conflict of interest, real or apparent, arising from the fact that NIH (RAC's parent) is the same institution that funds much of the gene therapy research that RAC reviews. NIH's interest in promoting the fruits of the research it funds may conflict with its responsibility to approve or deny human protocols based on other considerations. In addition, RAC members are appointed by NIH, so RAC members might also feel beholden to NIH, regardless of any prior biases, which could cause them to lean toward approval of protocols.[11] Whether these conflicts have a real effect or not, they are best avoided.

### *National Review*

Despite the flaws discussed above, the national RAC review process has proven itself highly rigorous and public. Most analysts commend the dual local-national review process used for somatic cell gene transfer protocols under the RAC.[12] While local review serves important goals in protecting the subjects of human research and preventing biohazards,[13] a national review process is also appropriate for research sure to engender a national debate. In the case of somatic cell gene transfer, the national review has added credibility to the review process. Gene therapy is a "hot" area of science, and has been for almost two decades. Those involved in it are likely to be regarded as "stars" in their respective local institutions, drawing national attention and attracting ample research funds. Given these facts, a purely local review can be subject to skepticism because the interests of the local institution are aligned with those of the research "star." In addition, the esoteric expertise necessary to conduct a review may be difficult to find locally. A national review, in contrast, can involve highly expert technical review and reviewers who are independent of those local interests.[14] A national reviewing body may also provide more opportunity to represent diverse interests than a local review could provide.

### *Preemption*

We have recommended establishing a standing body that will conduct prospective reviews of studies proposing IGM. We are seeking to address many of the problems we see in the current regulatory framework as it has been applied to somatic cell gene transfer. We also recommend that the legislation establishing this standing body and review process should expressly preempt state and local rules (court cases, regulations, statutes). This will help avoid the same type of confusing patchwork of laws that exists now with respect to embryo research.[15]

Preemption is based on the U.S. Constitution's supremacy clause, which makes federal law the "supreme law of the land." Where the U.S. Congress has declared that it is expressly preempting state law, where preemption can be implied from a statute, or where state law actually conflicts with federal law, state regulation of a given area is precluded. Congress has expressly preempted state actions in analogous areas such as the field of medical devices.[16]

Leaving decisions about IGM to a legal system of varying court decisions and inconsistent state legislative enactments would create long periods of great uncertainty about what is permitted, what is not, and the consequences of violating norms. It would also likely be slow and inefficient and produce different policies in different jurisdictions.

## Current Limits

We have divided the legal norms that have the potential to apply to inheritable genetic modifications in the United States into five different types:

1. Common law
2. National Institutes of Health (NIH) Recombinant DNA Advisory Committee (RAC) guidelines, and "Points to Consider" (these requirements apply whenever an institution accepts NIH recombinant DNA research funds)
3. Health and Human Services regulations protecting research subjects at institutions that receive federal funds
4. Food and Drug Administration regulations and guidelines
5. Federal and state statutes governing research on embryos

### *Common Law*

When a federal or state court rules on a specific case and applies or interprets principles that were enunciated in previously published court decisions, it is using and extending the "common law." The common law is a body of principles, norms, and rules recognized and affirmed by courts that have their authority anchored in history, custom, and experience. In general, common law is the body of law developed through successive court decisions rather than the acts of legislatures or regulatory authorities. The sorts of common law principles that might apply to IGM include negligence precedents developed in the context of medical malpractice or other tort cases, decisions that have interpreted or augmented guidelines, regulations, or statutes, and contract doctrines.

In the context of IGM, it is easy to imagine disputes that could find their way into courts. Courts would apply common law principles and set new precedents that could affect the evolution of the technology. For example, imagine an IGM experiment similar to the experiment described in the consent form in Appendix A. A couple, both homozygous for Gaucher disease type II, are research subjects in a protocol designed to replace the faulty glucocerebrosidase gene that causes Gaucher disease with the normal gene in their early, developing embryos. Imagine that the protocol is successful and a healthy child is born to this couple. The child does not suffer from the same disease as her parents. However, when that child grows up and has children, her children are born with an anomaly that can be directly traced to the IGM experiments in which their grandparents participated. Perhaps these grandchildren suffer from limb deformities, or are infertile. If this bad outcome ended up as a lawsuit in court, the court would apply common law principles to the facts of this case.[17] For example, in order to determine whether the research investigators owed a duty of care to the grandchildren of the research subjects, the court might look at previous decisions which disallowed causes of action by granddaughters of women who ingested diethylstilbestrol (DES) during pregnancy, resulting in damage to their daughters' reproductive systems.[18] Under our current set of rules, in order to determine the standard of care to which the researchers would be held, the court would probably look to the RAC guidelines, "Points to Consider," and human subject protections, among other things. The outcome of the first IGM case would influence the next case and so on, as a body of case law developed regarding IGM.

### *NIH RAC Guidelines and "Points to Consider"*

Somatic cell gene transfer is governed in part by guidelines for recombinant DNA research[19] and "The Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules in the Genome of One or More Human Subjects" ("Points to Consider").[20] These rules have been amended several times in the past few decades.

Rules governing recombinant DNA research were first created in the mid-1970s. The first idea for splicing together DNA from different organisms arose in the late 1960s in the laboratory of Paul Berg at Stanford University.[21] When the idea was presented to scientists at a Gordon Scientific Conference in the summer of 1973, with a specific set of experiments soon in prospect, some became concerned that DNA changes performed in laboratory experiments might be incorporated into self-replicating organisms that could harm people, animals, and plants outside the laboratory. The concern for such biohazard was brought to the attention of other scientists in a 1973 letter to *Science*.[22] The number of investigators who had been thinking of carrying out such experiments was relatively small, and they were almost entirely funded by the National Science Foundation (NSF) and NIH. A number of meetings were held, most famously the one convened by the National Academy of Sciences at Asilomar, near Santa Cruz, California. A note urging observation of a moratorium, signed by respected scientists, was published in *Science* and *Proceedings of the National Academy of Sciences* in 1974.[23] The relatively small community of scientists contemplating gene-splicing experiments imposed a moratorium on themselves, agreeing not to do such experiments until there was some consensus about how to do them safely.[24]

Later, NIH asserted authority to oversee recombinant DNA research. It formed the RAC to formulate guidelines to avoid the dangers posed by biohazard. Over time, as experience accumulated and untoward biohazard proved less likely than initially feared, the guidelines were relaxed. The Recombinant DNA Advisory Committee later shifted its focus to human gene transfer experiments. The impetus to attend to human experiments came first from a recommendation in the 1982 report *Splicing Life,* by a presidential bioethics commission.[25] This new focus coincided with a dramatic reduction in the perceived need for biohazard protections. The transition from reviewing laboratory experiments for biohazard risk to reviewing clinical protocols for risks to the research participants required new expertise and a new set of guidelines. RAC's

essential functions were, however, carried from laboratory biohazard to human gene transfer. RAC prepared its own guidelines and it retained approval authority over proposed research protocols. In January 1985, the "Points to Consider in the Design and Submission of Human Somatic-Cell Gene Therapy Protocols" were first published in the *Federal Register.* This document was intended to provide guidance for gene therapy researchers. The "Points to Consider" ask researchers to respond to more than 100 questions related to outcomes or consequences of a disease, alternative treatments, and the proposed genetic intervention, as well as questions related to fairness, justice, and autonomy.[26] RAC's approval authority was removed in 1995, but if it were now restored, the history of successful transition in the RAC function of the early 1980s suggests RAC could evolve into the review body we propose in the recommendations above.

Compliance with both RAC biohazard guidelines and the "Points to Consider" was obligatory for institutions receiving federal recombinant DNA research funds. The incentive for compliance was mainly the threat of losing federal funding and risk to one's professional reputation. At the time, NIH and NSF (which jointly funded the initial recombinant DNA experiments carried out by Herbert Boyer and Stanley Cohen)[27] funded almost all recombinant DNA research, so this was a potent threat. A majority of health R&D is now funded in the private sector. A threat to withdraw federal funds can no longer restrain an entire field of study as it could recombinant DNA research in the 1970s, when NSF and NIH were far and away the largest funders of such research. Since 1980, private R&D funding has exceeded federal funding.[28]

The RAC "Points to Consider" excludes IGM from consideration: "The RAC will not at present entertain proposals for germ line alterations."[29] If an IGM experiment involved the use of recombinant DNA in an institution receiving federal funds for recombinant DNA research, RAC guidelines and "Points to Consider" would apply, and IGM would presumably be disallowed unless the "Points to Consider" were altered. RAC itself could, however, change this language, stipulating that if a protocol for IGM were proposed, it would be subject to an extensive review process.

### *Human Subject Protections*

Protections for individuals participating in research trace their origins to the Nuremberg Code written after the Doctors' Trial in 1949.[30] Such protections are embodied in federal regulations.[31] The regulations cover institutions that

have a formal agreement with the federal government that binds them to abide by the "common rule," the usual name for Title 45, Section 46, of the *Code of Federal Regulations*. Those regulations apply to the Department of Health and Human Services and sixteen other federal departments and agencies. (FDA has a separate set of regulations; see below.) Any institution that receives federal grants and contracts from all but a few agencies (most of which conduct little research) must have a federalwide assurance, which commits the institution that receives federal funds to abide by the human subject protections, including an agreement to establish an IRB to review and approve research protocols that involve human participants and to report any violations that come to its attention.

Protocols to get approval for testing drugs, biologics, or devices from the FDA are also subject to IRB review. This extends parallel regulations to cover private firms and institutions submitting data to FDA for approval, even if they do not use federal funds for the research (21 CFR 50 and 56).[32]

The conceptual framework for the federal human subject protection regulations is the work of the National Commission for the Protection of Biomedical and Behavioral Research, the first national "bioethics commission," which operated from 1974 to 1978.[33] The seminal document, to which every federalwide assurance explicitly refers, is the Belmont Report, which the National Commission wrote to crystallize its findings from a series of reports on different populations and different types of research. The Belmont Report laid out three general principles to guide judgments about whether research is ethically justified: respect for persons, prospect of benefit, and assurance of justice.[34]

Federal human subject protections would likely apply to IGM research if the research occurred in an institution receiving federal funds or if the IGM research came under FDA jurisdiction. Federal human subject protection regulations cover most medical research in the United States, but there are some areas that are not covered. Studies considered "innovative therapy" or "experimental treatment" can fall outside IRB review. This is most apt to occur with novel surgical or other procedures that do not entail use of an unapproved drug or device according to FDA rules. If such treatment is conducted with only a few individuals and in a way that does not fall under the regulatory definition of "research," such work can take place without IRB review.[35] Even work clearly falling under the definition of research could go forward without IRB or FDA review if it were carried out by an institution that did not use federal funds and did not have a standing Federal Assurance agreement, and if it did not involve

an unapproved drug or device subject to FDA jurisdiction.[36] Many of the technologies that may prove relevant to IGM have been developed in private fertility clinics. Many of these clinics have some form of review, but many have been deliberately structured to avoid IRB review under federal regulations. If the institutions involved in early studies of IGM are private fertility clinics, early IGM research could fall outside current federal regulations protecting human subjects participating in research.[37]

### *Food and Drug Administration Regulations*

The FDA is the primary home of current federal government regulation of somatic cell gene transfer research. Whether the FDA would have jurisdiction over all types of IGM is an open question.

The FDA Center for Biologics Evaluation and Research[38] published a guidance document that "represents the agency's current thinking on the development and regulation of somatic cell therapy products," including somatic cell gene therapy.[39] This guidance document defines the types of somatic cell and gene therapies that will be evaluated by the FDA. The document also directs readers to the regulatory considerations for somatic cell and gene therapy, and it establishes scientific standards against which the safety and efficacy of gene transfer protocols will be tested. However, "the document does not discuss genetic manipulation aimed at the modification of germ cells."[40] This guidance document thus explicitly excludes IGM from its purview. The FDA has, however, asserted jurisdiction "over human cells used in therapy involving the transfer of genetic material by means other than the union of gamete nuclei." This assertion of jurisdiction includes, but is not limited to, "cell nuclei (e.g., for cloning), oocyte nuclei, ooplasm, which contains mitochondrial genetic material, and genetic material contained in a genetic vector, transferred into gametes or other cells." According to a July 6, 2001 Letter to Sponsors/Researchers, "the use of such genetically manipulated cells (and/or their derivatives) in humans constitutes a clinical investigation and requires submission of an Investigational New Drug application (IND) to the FDA."[41] In addition, the FDA had previously published a "Tissue Action Plan, Reinventing the Regulation of Human Tissue," in which it asserts "tissues and cells processed such that their biological or functional characteristics may have been altered (or were intentionally altered) . . . would require FDA review for safety and effectiveness."[42] The FDA's assertions of jurisdiction seem to cover IGM, whether in gametes, zygotes, or preembryos.

If an IGM protocol were in the works, would the FDA's jurisdiction actually extend to genetic manipulation of zygotes or preembryos that will result in the modification of germ cells of the next generation? Gene transfer products that rely on viral vectors fit nicely within the statutory definition of "biological product" and are therefore subject to FDA regulation. The definition of "biological product" is "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings."[43] Somatic cell gene transfer products that do not involve viruses, such as directly administered DNA or DNA-liposome mixtures, come under FDA jurisdiction as "analogous products" or as drugs.[44]

Lori Andrews has pointed out, however, that cloning might not fall within the FDA's jurisdiction because the tissue alteration guidelines "may not technically extend to cloning, and even if they do, they do not require prior approval if a patient's cells are being used for his or her own reproductive purposes."[45] The IGM we are currently contemplating, involving genetic manipulation of gametes, a zygote, or preembryo with subsequent transfer to a mother for gestation, might be considered closer to cloning or to intracytoplasmic sperm injection than to somatic cell gene transfer for the purposes of FDA jurisdiction. Moreover, DNA repair methods that currently seem necessary to permit safe IGM would cause reversion to a known genotype, and could arguably be excluded because they are not "alterations" but reversions. Thus, there may be some question about whether the FDA would actually have jurisdiction over IGM without some legislative or regulatory action.

If the FDA does have jurisdiction over IGM, then under rules in place today and given our expectations about what IGM technologies will look like, IGM likely would be subject to FDA review as a biologic product. According to current practices, somatic cell gene transfer is similarly treated as a biologic product, and goes through the following steps on its way to approval for a product license. First, before an investigational new drug (IND) application is submitted, FDA's Center for Biologics Evaluation and Research encourages meetings between the sponsors planning the clinical trials and the center.[46] The FDA does some educational outreach aimed mainly at the scientific and industrial communities. The "sponsors present the rationale [to the center] for a particular approach, present preclinical data, discuss proposed trial designs, and otherwise describe their concepts and development plans. In the context of the

specific product, the center's scientists describe standards for product characterization and quality control, comment on research strategies, pinpoint potential manufacturing problems, and suggest revisions in preclinical or clinical protocols."[47] The pre-IND requirements include testing the product in the laboratory and providing that data to the FDA, preclinical animal studies, and the provision of a draft clinical protocol. Formal IND applications must include safety data sufficient to persuade the FDA to give permission for human studies. Applications "must contain information on product manufacturing and testing to ensure that trial subjects will not be exposed to an unreasonable and important risk of illness or injury. . . . The FDA focuses on the development of safe and effective biologic products, from their first use in humans through their commercial distribution."[48]

FDA's review focuses on the safety and efficacy of the protocol, which are important considerations. The FDA does not, however, address the sweeping issues of justice, consequences for society, or moral principles. In addition, FDA review of gene transfer protocols is conducted in private (although following the death of Jesse Gelsinger, NIH and FDA clarified reporting of adverse events, with provisions that could lead to more information about them becoming public).[49] The public has no input into the process of review, and might not even know any experiments are under way, although some forms of genetic modification would be subject to the NIH-FDA agreement that calls for explicit public discussion of gene transfer experiments. DNA repair methods would arguably fall outside that agreement.

Whenever public review and input is deemed necessary, the protocol in question is referred to the NIH RAC. If an IGM protocol came to the FDA under present procedures, it would likely be placed on "clinical hold" (meaning no patients could be enrolled in the study).[50] Through established procedures, the FDA would verify that the RAC had received it. The RAC, with its public review processes and scrutiny of issues relevant to larger society, would take over from there, with FDA review commencing once the social and ethical issues were approaching resolution and technical criteria began to carry more weight in the approval decision. However, the "Points to Consider" would need to change before the RAC would even entertain IGM protocols. The process we sketch here depends on speculation about how FDA and NIH would treat an IGM proposal. If IGM technologies mature enough to make IGM realistic, then NIH and FDA will have to develop new policy and formally clarify how such protocols will be reviewed.

### *Embryo Research Laws*

Given the current state of technology, it is likely that initial IGM protocols will involve the manipulation of embryos rather than gametes to gain access to the germ line. Therefore, restrictions on embryo research will probably govern IGM as well. After a long, de facto, controversial moratorium on the provision of federal funds for embryo research, Congress added the Dickey-Wicker amendment to the Health and Human Services appropriations law in 1996 and has retained it in every subsequent annual appropriation and continuing resolution through 2003, forbidding the use of federal funds for "research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero." For purposes of this restriction, "the term 'human embryo or embryos' include any organism, not protected as a human subject [elsewhere in the *Code of Federal Regulations*] . . . , that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells."[51] Although this law effectively prevents embryo-based IGM research in any institution that receives federal funds (precluding such research in most major academic research institutions), it does not proscribe embryo research in private institutions.

Several states have enacted laws prohibiting or regulating embryo research.[52] These laws apply to the private as well as the public sector. Some of these state statutes explicitly apply to research in preembryos or early embryos.[53] Many are directed at cloning, fetal experimentation, or abortion, but apply to IGM research in preembryos expressly or by implication.[54] Many of the state statutes that prohibit embryo research make exceptions for research that is intended to be therapeutic either for the mother or for the individual resulting from the procedures.[55] Presumably, then, IGM research beyond early phase-1-type safety trials would be allowed under many of these statutes. How IGM research could proceed to the therapeutic stage without passing through a safety phase is an unanswered question.

The state statutes are inconsistent in their terminology and substance. For example, a New Hampshire surrogacy statute provides that "I. No preembryo shall be maintained ex utero in the noncryopreserved state beyond 14 days postfertilization development. II. No preembryo that has been donated for use in research shall be transferred to a uterine cavity."[56] This New Hampshire statute has the effect of disallowing IGM research involving preembryos. A Rhode Is-

land law prohibiting human cloning, on the other hand, provides "nothing in this section shall be construed to restrict areas of biomedical, microbiological, and agricultural research or practices not expressly prohibited in this section, including research or practices that involve the use of . . . gene therapy."[57] The Rhode Island law explicitly allows gene therapy research involving preembryos. Given the inconsistencies in language and content of the embryo research rules from one state to the next, existing limits will not provide coherent treatment of IGM research protocols that involve embryo transfer of DNA.

## Conclusion

The current limits governing gene therapy, which could theoretically apply to IGM proposals, are inadequate to deal with IGM. The flaws that have been revealed as these rules and procedures have been used for somatic cell gene transfer could prove even more troublesome for governing IGM experiments. The model we have proposed resolves many of these problems and forestalls new ones that may be associated with IGM.

If the time arrives, however, at some point in the future, when IGM is no longer an experimental procedure, there are potential dangers in maintaining a centralized regulatory system. The regulatory system we have proposed applies to IGM research. It would not be appropriate as a decision maker about which nonexperimental IGMs should be allowed. Establishing and enforcing rules about nonexperimental IGMs would require determinations about which human characteristics should be created or enhanced and which should not, about "what sort of people should there be."[58] Government control of human characteristics can be dangerous. One need look back only as far as the early-twentieth-century eugenics programs to be reminded of the dangers. Regulation of IGM in the long term presents independent and perhaps deeper issues that must be considered separately from the issues presented by IGM in its experimental phase.

### NOTES

1. More about the RAC history will be presented below.

2. This case was settled out of court by the Foundation on Economic Trends and NIH on terms that permitted the experiments to go forward, but the exact terms of the

agreement are not known because it included a "gag" provision barring the parties from disclosing its terms publicly.

3. Robert M. Cook-Deegan, *Do Research Moratoria Work?: A Review of Fetal Research, Gene Therapy, and Recombinant DNA Research* (Washington, D.C.: National Bioethics Advisory Commission, 1997).

4. The infraction came to light when someone called Nicholas Wade, a reporter for *Science,* who ran an article about it in September 1977 (Nicholas Wade, "Recombinant DNA: NIH Rules Broken in Insulin Gene Project," *Science* 197 [1977]: 1342–45.) Wade's calls to NIH to ask for information about the case provoked an investigation by the UCSF biosafety committee and by NIH's Office of Recombinant DNA Activities. Those inquiries concluded that there had indeed been infractions of the RAC guidelines. Both UCSF and NIH relied heavily on an October 14, 1977 memo to Dr. James Cleaver, chair of the Biosafety Committee University of California San Francisco, prepared by Howard Goodman and William Rutter, directors of the two relevant UCSF laboratories, who stated that the clones had been destroyed. This was the same conclusion reached by Stephen Hall in his book about the cloning of the insulin gene, although Hall noted that there were some residual doubts about whether all the clones and all the DNA derived from those original clones were actually destroyed (Stephen S. Hall, *Invisible Frontiers: The Race to Synthesize a Human Gene* [New York: Atlantic Monthly Books, 1987]). In a federal district court trial arising from patent litigation between the University of California and Eli Lilly (*University of California v. Eli Lilly and Co.* 1996. MDL Docket No. 912, No IP-92-0224-C-D/G, decided December 11, 1995. U.S. *Patent Quarterly* 39 USPQ2d 1225, 1248–1254 [S. D. Ind. 1995], aff'd in part, rev'd in part 119 F.3d 1559 [Fed. Cir. 1997]), this account was cast into doubt when registered letters between Rutter and Goodman were found. The judge in that case found the UC scientists' account "not credible," but a subsequent decision by the Court of Appeals, Federal Circuit found the judge had "abused his discretion" in using his findings of fact about UCSF using DNA outside the RAC guidelines to judge the patent unenforceable. (In another part of the ruling, the patent's claims were judged not to encompass human insulin, making it far less valuable.) (www.law.emory.edu/fedcircuit/july97/96-1175.html; 119 F.3d 1559; 1997 U.W. App. LEXIS 18221; 43 U.S.P.Q.2d [BNA] 1398.) Several conclusions can be reached about the UCSF infraction, although many of the facts will remain uncertain unless and until those directly involved clarify (and document) the events. Most important, the infractions did not pose an increase in biohazard; quite the reverse. The controversy was instead about how quickly NIH certified the vectors, what evidence was needed, and the rules for competition among scientists. In the end, what was most at stake was fair competition among molecular biologists rather than public safety, whether UCSF research teams "jumped the gun" on competing scientific groups at Harvard and City of Hope Hospital.

5. The facts of the case remain obscure more than two decades after the events, largely because UCSF and NIH both failed to carry out credible investigations. The files at the NIH Office for Recombinant DNA Activities contain no first-person accounts from the individuals who actually carried out the experiments, and the decisions by NIH and UCSF appear to rely heavily on the account in a summary memo written by the directors of the laboratories whose activities were being investigated (Office of Recombinant DNA Activities, case file on William Rutter, University of California San Francisco, 1978). Further documents came to light two decades later only through the

extensive discovery process associated with the insulin patent litigation. The interests of all concerned, including those whose actions were questioned as well as UCSF and NIH, would have been much better served by a thorough, independent, and credible investigation.

6. The case was *University of California v. Eli Lilly and Co.* The pertinent findings are summarized in the district court judge's opinion (U.S. Patent Quarterly 2d, Book 39, from "A. The '525' Patent" on pp. 1248–54) and in *Science* (Eliott Marshall, "Scientific Community: A Bitter Battle over Insulin Gene," *Science* 277 [August 22, 1997]: 1028–30).

7. Daniel J. Kevles, *The Baltimore Case: A Trial of Politics, Science, and Character* (New York: W. W. Norton, 1998).

8. Reports from June 1998 and 1999 are summarized in a statement by George Grob before the House Committee on Government Reform, Subcommittee on Criminal Justice, Drug Policy, and Human Resources.

9. "In gene therapy trials, what is an 'adverse event'? When should it be reported to what agency or agencies with what information held private?" Washington Fox, December 13, 1999.

10. "FDA Orders Tighter Watch over Safety in Gene Therapy Tests," *Chicago Tribune,* March 8, 2000, 3, and "Advisory Panel on Gene Therapy Research Deadlocks," *Chicago Tribune,* March 10, 2000, 8. FDA's proposed rule for publicly reporting adverse events for gene transfer and xenotransplantation research: www.fda.gov/cber/rules/ frgene011801 .htm ( January 18, *Federal Register*). The agreement between OBA (at NIH) and FDA to share adverse events data is: www.fda.gov/cber/regsopp/91102.htm. And the FDA's generic adverse event program MedWatch is: www.fda.gov/medwatch/index.html.

11. On the other hand, there is also the concern that RAC members may themselves be involved in gene transfer research and therefore have competitive reasons to deny approval of protocols.

12. LeRoy Walters and Julie Palmer, *The Ethics of Human Gene Therapy* (New York: Oxford University Press, 1997).

13. See below for more on human subjects protections.

14. Controversy surrounding reviews of early somatic cell gene transfer, for example, included concern that scientists involved in the review were known scientific competitors who could gain only by disapproval, not approval, of a protocol, the reverse of the presumption in local review. In a review process intended to allay national public concerns, this problem of national review by competitors is preferable to lenient review by a local review board.

15. See below for more on embryo research as it relates to gene transfer and IGM.

16. Medical Devices Amendments to the Food, Drug and Cosmetics Act, 21 U.S.C. § 360k(a). See also *Medtronic, Inc. v. Lohr,* 518 U.S. 470, 1996.

17. For more on a similar scenario, see Julie Gage Palmer, "Human Gene Therapy: Suggestions for Avoiding Liability," Gene Therapy for Neoplastic Diseases, *Annals of the New York Academy of Sciences* 716 (1994): 294–306.

18. *Enright v. Eli Lilly & Company,* 568 N.Y.2d 550 (N.Y. Feb. 19, 1991) (holding that strict products liability does not extend to grandchild whose premature birth allegedly resulted in damage to mother's reproductive system caused by her in utero exposure to DES); *Sorrells v. Eli Lilly & Company,* 737 F.Supp. 678, 679 (D.D.C. 1990) (holding that DES manufacturer owed no duty to unborn granddaughter of person who ingested DES). For more detailed discussion of preconception duty and collected cases, see J. G.

Palmer, "Liability Considerations Presented by Human Gene Therapy," *Human Gene Therapy* 2 (1991): 235–42.

19. www4.od.nih.gov/oba/aboutrdagt.htm.

20. www4.od.nih.gov/oba/guidelines.pdf.

21. Sheldon Krimsky, *Genetic Alchemy: The Social History of the Recombinant DNA Controversy* (Cambridge, Mass.: MIT Press, 1982).

22. Maxine Singer and Dieter Soll, "Guidelines for Hybrid DNA Molecules," *Science* 181 (September 21, 1973): 1114.

23. Paul Berg et al., Summary Statement of the Asilomar Conference on Recombinant DNA Molecules, *Proceedings of the National Academy of Sciences USA* 72 (June 1975a): 1981–84; "Summary Statement of the Asilomar Conference on Recombinant DNA Molecules," *Science* 72 (June 6, 1975): 991; Paul Berg et al., "Potential Biohazards of Recombinant DNA Molecules," *Proceedings of the National Academy of Sciences USA* 71 (July 1974a): 2593–94, and "Potential Biohazards of Recombinant DNA Molecules," *Science* 185 (July 26, 1974): 3034.

24. The voluntary moratorium is generally lauded as a success, as no one is known to have violated it. Most accounts assume that the moratorium was universally observed. It may have been, but there was no way to detect any infractions, no mechanism to report them, and little incentive to do so. A self-imposed moratorium was unprecedented, and over time some scientists began to chafe under the restrictions. The moratorium certainly restrained work on recombinant DNA for a period, but probably would not have been sustained for many more months without the next step of NIH oversight through RAC.

25. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *Splicing Life* (Washington, D.C.: U.S. Government Printing Office, 1982).

26. See Walters and Palmer, *The Ethics of Human Gene Therapy,* 148–50.

27. U.S. Patents 4,237,224, 1980; 4,486,484, 1984; and 4,740,470, 1984.

28. National Science Board, *Science and Engineering Indicators—2002,* NSB 02-1 (Arlington, Va.: National Science Foundation, 2002).

29. LeRoy Walters and Julie Palmer, "Points to Consider," in *The Ethics of Human Gene Therapy,* 172. Also www4.od.nih.gov/oba/guidelines.pdf (NIH guidelines) and www4.od.nih.gov/oba/apndxm.htm ("Points to Consider").

30. George J. Annas and Michael A. Grodin, *The Nuremberg Code in U.S. Courts: Ethics versus Expediency* (New York: Oxford University Press, 1992), 201–22; Leonard H. Glantz, "The Influence of the Nuremberg Code on U.S. Statutes and Regulations," in Annas and Grodin; and Michael A. Grodin, *Historical Origins of the Nuremberg Code,* in Annas and Grodin.

31. 45 CFR 46.

32. http://www.fda.gov/oc/ohrt/irbs/default.htm (accessed September 14, 2002).

33. The history of these protections is summarized by the Office of Technology Assessment (U.S. Congress, 1993), and the Institute of Medicine. Ruth Ellen Bulger, Elizabeth Meyer Bobby, and Harvey V. Fineberg, eds., *Society's Choices: Social and Ethical Decision Making in Medicine, Institute of Medicine* (Washington, D.C.: National Academy Press, 1995), and U.S. Congress, Office of Technology Assessment (Robyn Y. Nishimi, Project Director), *Biomedical Ethics in U.S. Public Policy: Background Paper,* OTA-BP-BBS-105 (Washington, D.C.: U.S. Government Printing Office, June 1993); and

extensively reviewed by the Advisory Committee on Human Radiation Experiments (tis.eh.doe.gov/ohre/roadmap/achre/index.html) in a final report (tis.eh.doe.gov/ohre/roadmap/achre/publication_info.html) (Washington, D.C.: U.S. Government Printing Office, 1995); see also supplements 061-000-00850-1, 061-000-00851-9, and 061-000-00852-7.

34. National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research, U.S. Department of Health, Education, and Welfare, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (Washington, D.C.: U.S. Government Printing Office, 1978).

35. See OPRR Report 95-02, "Exempt Research and Research That May Undergo Expedited Review" from Office of Protection from Research Risks, National Institutes of Health, May 5, 1995. grants.nih.gov/grants/oprr/humansubjects/guidance/hsdc95-02.htm; the relevant regulatory language is found at 45 CFR 46, section 110.

36. The expansion of federal human subject protections to privately funded research was contemplated by the 106th Congress. Several bills were introduced in the House of Representatives—HR 3569, HR 4605—but were not adopted.

37. More on FDA jurisdiction over genetic manipulation of embryos is presented below.

38. The Food and Drug Administration is divided into several centers. Somatic cell gene transfer comes under the jurisdiction of the FDA Center for Biologics Evaluation and Research, which is further divided into six offices, including the three substantive Offices of Blood, Vaccines, and Therapeutics Research and Review. There are five divisions within the Office of Therapeutics Research, including the Division of Cellular and Gene Therapies. Somatic cell gene transfer is reviewed by the Division of Cellular and Gene Therapies.

39. Guidance for Industry, Guidance for Human Somatic Cell Therapy and Gene Therapy, which can be found at www.fda.gov/cber/guidelines.htm (accessed September 14, 2002).

40. Ibid.

41. www.fda.gov/cber/1tr/cytotrans07601.htm (accessed September 14, 2002).

42. Tissue Action Plan (updated November 8, 1999), available at www.fda.gov/cber/tissue/tissue.htm, 8 (accessed September 14, 2002).

43. 42 U.S.C. §262 (i).

44. "The term drug means . . . (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals" 21 USC §321(g); D. A. Kessler et al., "Regulation of Somatic-Cell Therapy and Gene Therapy by the Food and Drug Administration," *New England Journal of Medicine* 329 (October 14, 1993): 1169–73.

45. Lori Andrews, "Is There a Right to Clone?: Constitutional Challenges to Bans on Human Cloning," *Harvard Journal of Law and Technology* 11 (1998): 643–81. In footnote 102 of that document, "for example, if the FDA can regulate cloning, why hasn't it used the same authority to monitor intracytoplasmic sperm injection ('ICSI'), in which DNA (in the form of sperm) is being injected into women's eggs?"

46. Kessler et al., "Regulation of Somatic-Cell Therapy and Gene Therapy by the Food and Drug Administration."

47. Ibid., 1172.

48. Ibid., 1171–72.

49. "Investigators who have received authorization from FDA to initiate a human gene transfer protocol must report any serious adverse event immediately to the local Institutional Review Board, Institutional Biosafety Committee, Office for Human Research Protections (if applicable), and NIH OBA, followed by the submission of a written report filed with each group. Reports submitted to NIH OBA shall be sent to the Office of Biotechnology Activities, National Institutes of Health" (Appendix M-I-C-4, htttp://www.fda.gov/ohrms/dockets/ac/01/briefing/3794b3_11.pdf [accessed September 20, 2002]; also FDA letter to gene transfer investigators, November 5, 1999, http://www.fda.gov/cber/1tr/gt110599.htm [accessed September 20, 2002]). Some of those data reported to NIH may be made public. "When information submitted in serious adverse event reports and annual reports is labeled trade secret or confidential commercial information, the NIH OBA will assess this claim and make a determination. If NIH OBA determines that the data so labeled are confidential commercial or trade secret and that their public disclosure would promote an understanding of key scientific or safety issues, the NIH OBA will seek agreement from the appropriate party to release such data" (DHHS, NIH, Office of Biotechnology Activities, "Actions under the NIH Guidelines," *Federal Register* 66, no. 223 [November 19, 2001]: 57970).

50. One basis for clinical hold is "inadequate information to assess risk to patients."

51. 111 Stat 1467, sec. 513. A current version of this provision can be found at 107 P.O. 116; 115 stat. 2177, sec. 510 ( January 10, 2002).

52. See, for example, La. Rev. Stat. Ann. §9:121–122 (2001); Mass. Gen. Laws Ann. Ch. 112, §12J (2001); Mich. Comp. Laws Ann. §333.2685-.2692 (2001); Minn. Stat. §145.421-.422 (2001); N. D. Cent. Code §14-02.2-02 (2002); N. H. Rev. Stat. Ann. §168-B:15 (2002); 18 Pa. C. S. §3216 (2002); R.I. Gen. Laws §11-54-1 (2001). Three state statutes banning fetal research have been challenged in court and in all three challenges the statutes have been struck down as unconstitutionally vague. See *Jane L. v. Bangerter,* 61 F.3d 1493, 1499–1502 (10th Cir. 1995), rev'd on other grounds sub nom. *Leavitt v. Jane L.,* 518 U.S. 137 (1996); *Lifchez v. Hartigan,* 735 F. Supp. 1361, 1364–67 (N.D. Ill. 1990), aff'd mem., 914 F.2d 260 (7th Cir. 1990); *Margaret S. v. Edwards,* 794 F.2d 994, 999 (5th Cir. 1986).

53. See, for example, Mass. Gen. Laws Ann. Ch. 112, §12J (2001); N. H. Rev. Stat. Ann. §168-B:15 (2001); La. Rev. Stat. Ann. §9:121–122 (2001).

54. See, for example, R.I. Gen. Laws §11-54-1 (2001); Mich. Comp. Laws Ann. §333.2685-.2692 (2001).

55. See, for example, Mass. Gen. Laws Ann. Ch. 112, §12J (2001); R.I. Gen. Laws §11-54-1 (2001).

56. N. H. Rev. Stat. Ann. §168-B:15 (2002).

57. R. I. Gen. Laws §23-16.4-2 (2001).

58. This phrase is the title of a thought-provoking book that addresses, among other things, how decisions about nonexperimental human genetic engineering ought to be made. Jonathan Glover, *What Sort of People Should There Be?: Genetic Engineering, Brain Control and Their Impact on the World* (New York: Penguin Books, 1984).

CHAPTER EIGHTEEN

# Designing Tomorrow's Children

## The Right to Reproduce and Oversight of Germ-Line Interventions

Cynthia B. Cohen, Ph.D., J.D.

Advances in genetics and reproductive medicine promise to extend our choices beyond whether and when to create children to what sorts of children to create. Today we can avoid having certain sorts of children by analyzing the genes of embryos in vitro and implanting only those that appear disease-free or carry desired traits, while discarding the rest. In the near future, geneticists predict, we will gain the power to create certain children by altering or replacing genes found in embryos by means of germ-line interventions. Should these interventions become a reality, our choices about what kinds of children to create will take a new turn. Germ-line technology will extend the time line for choosing what sorts of children to have farther into the future, enabling us to select not only the genes of tomorrow's children, but also of their children and their children's children.

Decisions about the use of germ-line interventions will necessarily be linked to choices about reproduction, for these interventions require the use of in vitro fertilization. Germ-line interventions will therefore implicate a right introduced into legal and ethical parlance relatively recently—the right to reproduce. This right is said to protect from state interference not only the

choices of couples and individuals about whether to avoid reproduction, but also their affirmative attempts to reproduce.

The thrust of this chapter is to argue that our growing power to select the genes and many of the characteristics of tomorrow's children raises significant ethical and social challenges that require public discussion and, ultimately, public oversight. Among these are how we should carry out our obligation to protect the safety and welfare of our children and their descendants and whether selective interventions into the germ line for purposes of enhancement would collectively amount to a contemporary form of eugenics. The right to reproduce, I maintain, does not protect individual uses of germ-line interventions from state oversight. This does not mean that individuals and couples should have no say about whether to use these interventions in the future. It means that society has a responsibility to address the public policy questions raised by germ-line technology and to impose restrictions on its use when necessary to protect tomorrow's children and to uphold foundational social values.

The ethical and social challenges that germ-line interventions pose point to the need for anticipatory public discussion of standards that should govern their acceptance and use. The significance of these challenges, I maintain, also makes clear the importance of establishing a publicly appointed group to review germ-line research protocols and to recommend flexible guidelines for the development and clinical use of this technology in both the public and private sectors. This oversight body should include among its purposes assuring the public that the risks that germ-line interventions might pose to tomorrow's children and future generations are being carefully assessed and that values fundamental to our constitutional democracy are being protected.

## The Right to Reproduce and Germ-Line Interventions

The use of germ-line interventions would involve inserting a gene directly into the human egg, sperm, or early embryo, thereby affecting its developing reproductive cells. The most likely scenario is that a human egg would be fertilized in vitro and that genetic modifications would be introduced into the resulting embryo that would be integrated into all the chromosomes of all of its cells, including its germ or reproductive cells. The embryo would then be implanted in the uterus of a woman and, if the pregnancy were carried to term, would emerge as a child with an altered genetic composition. That child would

go on to transmit its altered genes to its children who, in turn, would pass them along to future generations.

In the current state of scientific development, at least one of the new reproductive technologies, in vitro fertilization, would be needed in order to pursue germ-line interventions. The question of whether individuals and couples should be free to use this and other methods of assisted reproduction without state interference is said by some to have been answered in the affirmative by the U.S. Supreme Court. They argue that the high court has enunciated a right to reproduce that not only retains a sphere of personal choice for coital reproduction, but also protects individuals who wish to use the new reproductive and germ-line technologies from state intervention unless their choices would materially harm others. This is the position taken by a leading legal scholar in the area of reproductive law, John Robertson. In his book, *Children of Choice: Freedom of Choice and the New Reproductive Technologies,*[1] he draws together an ethical and legal framework for addressing the scope of personal choice in relation to reproduction. Later writings by Robertson embellish and alter in some respects the position he presents in that book.

Robertson recognizes that no right to reproduce is mentioned in the U.S. Constitution, but maintains that the 1942 Supreme Court case of *Skinner v. Oklahoma*[2] provides a precedent for the constitutional recognition of such a right (36). In that case, which involved whether a thrice-convicted chicken thief and armed robber should be forcibly sterilized, the Supreme Court held that the law requiring such sterilization was unconstitutional. Its holding was based on equal protection claims in that the state law required the sterilization of "habitual criminals" but not of embezzlers. The decision implies that if sterilization were carried out on criminals across the board, it would be an acceptable practice. The holding in *Skinner* does not provide a clear textual basis in support of a constitutional right of individuals to reproduce. It has never been reversed or revised. Moreover, the dicta cited by Robertson in this and related Supreme Court privacy cases are not legally binding. Still, many legal authorities would maintain that the reproductive privacy cases offer support for the claim that at least married couples have a right to reproduce coitally.

What does "a right to reproduce" mean? Robertson indicates in *Children of Choice* that it means that the exercise of "procreative liberty" or "the freedom to decide whether or not to have offspring and to control the use of one's reproductive capacity" (16) is presumptively protected from state interference. He supports such a right on the grounds that the very identity of people is

bound up with their desire to have or not to have a "reproductive experience." Their interest in self-determination requires others to respect their choice about this significant matter. Our notions of respect for autonomy and of the related requirement to protect such fundamental personal decisions as whether to beget and bear children permit state limitation of procreation only when it would involve substantial harm to others (40–41). While many commentators agree that the decision whether to have children is deeply significant and should be given considerable scope, it is still an open question whether the right to reproduce extends beyond coital reproduction to encompass the use of the new reproductive technologies.

Robertson argues that it does. He maintains that individuals should be free to make choices about whether to use technologically assisted reproduction without government restriction unless extremely strong justification for limiting their choices can be established. Such strong justification, Robertson claims, "is seldom present" (4). "In almost all instances an individual or couple's choice to use technology to achieve reproductive goals should be respected as a central aspect of people's freedom to define themselves through reproduction" (18).

Robertson goes on to declare that the right to reproduce encompasses not only the right to create a child, but also the right to create *a child of a certain sort* for rearing purposes (127). Thus, the right to reproduce incorporates a right to have access to "quality control devices," such as prenatal screening, preimplantation diagnosis, gene therapy, and germ-line interventions (33) in efforts to control offspring traits (17). Concerns about the effects of germ-line interventions on children who are conceived by such means and on future generations and about misuses of this technology for eugenic purposes, Robertson maintains, are too speculative to justify limiting the right of persons to employ this sort of genetic technology (163).

However, here at the edges of the right to control the traits of children, Robertson finds in *Children of Choice* that there are certain limits on what potential parents can do. Even though couples and individuals have a right to select from among a group of embryos based on health, gender, or other criteria meaningful to them (152–53, 156), not all of their desires related to reproduction are constitutionally protected, he maintains. Their right to use the new reproductive technologies and genetic interventions is limited by the requirement that their efforts must be directed toward the production of normal, healthy children.

Actions that aim to produce offspring that are more than normal (enhancement) "do not fall within procreative liberty because they deviate too far from the experiences that make reproduction a valued experience" (167). And actions that aim to produce offspring with diminished capacities are also not included within the provenance of procreative liberty (170). Thus, the desires of couples to use germ-line interventions to provide children with better than normal characteristics or to create children who are "less than healthy" are not among the core interests that fall under the umbrella of the right to reproduce Robertson indicates in his book.

The right to reproduce, on this view, incorporates an extensive bundle of rights. These include the right to use contraceptives, abort fetuses, engage in coital reproduction, employ the new reproductive technologies, discard embryos, hire surrogates, purchase semen, solicit and accept egg "donations," and apply germ-line interventions and other forms of "quality control" technologies to select and control the genetic makeup of future offspring for many purposes—except enhancement or diminishment. Thus the right to reproduce, for Robertson, is a global right that allows couples and individuals to do almost anything they desire related to reproduction.

This vast overextension of the right to reproduce is difficult to justify. The right to reproduce—rather, not to reproduce—is supported in Supreme Court cases on such grounds as the importance of bodily integrity, the integrity of the family unit, the intimacy of the marital relationship, being a parent and raising a child, and carrying on a genetic line.[3] These factors either do not apply or are only marginally related to a putative affirmative right to select and control the genetically based traits of one's offspring. Indeed, the interest in carrying on a genetic line could be denied by a right to select and control the traits of offspring. In short, a case needs to be made for an affirmative right to reproduce that extends as far as Robertson would take it and it would have to show that this right implicates many of these factors. Since Robertson has not yet developed such a case, we must conclude that germ-line interventions and other forms of genetic manipulation of children do not fall within the boundaries of a right to reproduce.

Robertson provides no justification for the few limits that he places on the use of germ-line interventions in *Children of Choice*. Since he finds that the right to reproduce entitles individuals to abort fetuses and discard embryos that are below par, it would seem appropriate to view it as also entitling them to create fetuses and embryos that are above par. Robertson apparently alters

his position and accepts this view in later work in which he declares that the right to reproduce does protect individual decisions to have children whose capacities have been enhanced. Thus, in a subsequent article he states that enhancement is one of the "easiest cases" to include under the right to reproduce, for its purpose is to benefit the child by reinforcing its positive characteristics.[4] Indeed, he concludes in this later article that intentional diminishment whereby, for instance, a deaf or dwarf child is deliberately created, also "would fall within the protective mantle of procreative liberty and only a showing of tangible harm to others would justify restriction."[5]

The welfare of the children who result from the use of in vitro fertilization and germ-line therapy does not figure prominently in this theory. It is the desires of would-be parents that fuel the right to reproduce and to employ germ-line interventions. Thus, even if these technologies were found to create great harm to children, Robertson maintains, this would not indicate that potential parents should be barred from using them. "If the child has no way to be born or raised free of that harm, a person is not injuring the child by enabling her to be born in the circumstances of concern," he states (75). Similarly, even if it were eventually shown that germ-line interventions would put later generations at risk, this would not provide grounds for prohibiting them because "but for the genetic alteration in question, later generations allegedly harmed without their consent may not have existed at all. Different individuals would then exist than if the germ line gene therapy had not occurred" (162).

The alternatives open to children and future generations, on this theory, are either existence in a seriously impaired state or nonexistence. They are better off existing, Robertson argues, for "a child's interests are hardly protected by preventing the child's existence" (75). This, as Bonnie Steinbock observes, is "procreative liberty gone mad," for it requires us "to facilitate the birth of children with horrendous, lethal diseases."[6]

Robertson's argument goes wrong because it misidentifies the subjects of germ-line interventions. They are not unconceived children waiting in the world of nonexistence, eager to enter this world, even if in a seriously impaired condition.[7] They are already conceived embryos that will, after germ-line interventions, be born as children with modified genes. If they are knowingly injured by such interventions after they have been created in vitro, it cannot be argued that this is ethically acceptable because, but for such interventions, they would not have existed. They would have existed, but, in all likelihood, in an uninjured state, if they had been allowed to proceed to birth. Consequently, those who introduce

germ-line changes into already created embryos, planning to bring them to term, and who knowingly damage them when they do so, make a wrongful choice. They put children-to-be into a worse state and, in so doing, harm them. Future generations are also harmed by injurious germ-line interventions, for without such interventions, other things being equal, they would have been born in an uninjured state. Descendants of injured children who inherit the injured state, therefore, are harmed by the initial germ-line intervention.

Robertson's view of the right to reproduce and to use germ-line interventions, which is currently the leading view, has broad public policy implications. It would bar government from regulating the uses to which individuals can put germ-line interventions unless these interventions would cause material harms to others—except the resulting children. Yet, as exhibited above, even if personal choices to design children using the new reproductive technologies were protected by a constitutional and moral right to reproduce, this right would not extend to germ-line interventions that allowed children to be injured in the process. As Massie observes, "the *optimal* (not minimal) well-being of children—is the appropriate basis upon which to shape social policy with regard to the use of assisted reproduction."[8] Invoking a right to reproduce does not provide ethical justification for maintaining that germ-line interventions should be almost exclusively a matter of personal choice. Extensive consideration must be given to whether such interventions would put at serious risk the welfare of tomorrow's children and of future generations.

## Major Public Policy Issues Raised by Germ-Line Interventions

When an activity that involves interventions into the genetic constitution of embryos might result in harm to the resulting children, this provides reason to oversee that activity. Such oversight is additionally justified when there is legitimate concern that significant social values would be jeopardized by this activity. To discern whether germ-line interventions would require greater oversight than is currently in place, I will therefore briefly examine (1) their potential impact on current and future generations and (2) their potential for reintroducing a form of eugenics.

### *Import for Current and Future Generations*

Germ-line interventions, if successful, would prevent serious hereditary disease from affecting not only our children, but also our grandchildren and their

children.[9] Surely it is right to repair genes associated with disease and disability in our children and their descendants if we can do so without seriously damaging our own well-being or sacrificing basic social goods and values. There is nothing logically or ethically incoherent about recognizing that we have obligations to future generations, even if we cannot identify the individuals who will constitute those generations.[10] While we need not attempt to produce the greatest possible good for future generations, we have an obligation to attempt to provide for their important needs.

In determining whether to proceed with germ-line interventions, we must weigh the significant benefits that have been postulated for these interventions against their possible risks. These include such risks as, for example, that manipulating the germ line might lead to harmful interactions between inserted or modified genes and other genes within the genome of the recipient embryo. Such outcomes, in turn, could create untoward and unanticipated harms to future children because an inadvertently introduced error would become a permanent part of a child's genetic legacy and affect generations to come after him or her.

How are we to assess the degree of risk that germ-line interventions pose? The sorts of risk/benefit calculations used to justify new treatments for those in the current generation cannot be applied accurately to future generations, since the cumulative damage that germ-line interventions might create would appear long after the original interventions had been completed. There is no way, in principle, to guarantee that germ-line interventions will not have unanticipated negative effects on descendants of those who receive them. Thus, the possibility of carrying out germ-line interventions raises major questions not only about the safety of children on whom they would be used in this generation, but also about the safety of subsequent generations of children.

Given this reality, it is arguable that we should not tamper with the germ line unless we can be certain that no harm would result to future generations. Since a total absence of risk could never be ensured, this would mean that germ-line interventions should never be employed. Yet this seems too stringent a standard to maintain in view of the fact that we allow some risks to be taken when we engage in experimental therapies in the current generation.

At the opposite extreme, it can be maintained, as Robertson does, that concerns about harm to future generations are "too speculative to justify denying use of a therapeutic technique that will protect more immediate generations of offspring" (162). Because those making decisions today about germ-line inter-

ventions cannot predict all risks that these pose to future generations, possible risks need not be taken into account, on this view. Yet it seems careless and contrary to the principle of nonmaleficence to ignore the possible harms to future children that this technology might create.

Let us consider an intermediate position about the degree of risk to future generations in assessing whether to carry out germ-line endeavors. Persons in different generations have duties and obligations to one another just as contemporaries do. John Rawls argues that the present generation should not simply do as it pleases, but is bound by the principles that would be chosen in the "original position" to define justice between persons at different points in time.[11] Rawls postulates that people in the "original position" (whose choices from behind the "veil of ignorance" are to constitute principles of justice) do not know to which generation they belong. Thus, using Rawls's approach, the question about the risks of germ-line interventions that we should ask is: What standard of risk would we choose if we knew we might exist in the future but did not know when or what our particular position and circumstances at that time would be?

I will sketch two possible answers here. One is that germ-line interventions should proceed in the current generation if ways of repairing genetic disorders that such interventions might create would be available in the future. This, however, seems an overly restrictive standard, for we might be willing to take the risk of incurring some degrees and sorts of harms to ourselves in the future in order to be rid of a gene related to a seriously deleterious condition.

A more adequate standard would be that (a) the risks of germ-line interventions for future persons, insofar as they can be known, should be no greater than their risk of being born with the genetic condition at issue and (b) that no germ-line interventions should be undertaken that *might,* to the best of our knowledge, create serious disorders in persons who would be born beyond the reach of those known risks. This two-pronged standard takes account of the incompleteness of our knowledge about future harms of germ-line interventions and yet allows some degrees of known harm if these would be no greater than that already in store for future generations. It also attempts to limit harms done to those in future generations who are outside the reach of those known risks.

### *Potential for Creating a New State or Privately Funded Eugenics*

The use of germ-line interventions selectively to enhance the intelligence, physical appearance, and even social behavior of future persons would open

the door to the creation of future generations of putatively superior or inferior individuals. If promoted and supported as a matter of public policy, this would amount to a new form of eugenics. Such a policy would raise significant ethical difficulties because it could lead to social devaluation of some on account of their genetic constitution. Once such changes were introduced and children of a certain sort became the socially accepted kind, any child who did not measure up in terms of health or looks would be considered flawed.

Moreover, children and their descendants would become the by-products of passing standards of beauty, athletic prowess, and intelligence. Paul Ramsey stated in the 1970s, "Medical practice loses its way into an entirely different human activity—manufacture (which most wants to satisfy desires)—if it undertakes to produce simply the desired sort of child."[12] Maura Ryan maintains that with the introduction of "quality control" measures, children would come to be seen as commodities designed to meet certain arbitrary standards, rather than as unique persons to be treasured for themselves.[13] Physicians and patients carrying out genetic screening, Marjorie Schultz declares, should be barred from search and destroy missions geared to "traits that particularly raise the most negative specter of eugenics—disadvantaging of unpopular groups on the basis of traits such as race, sex, intelligence, mild physical disability."[14]

Behind the concerns of these commentators is a belief that the introduction of genetic modifications for purposes of enhancement could reassert nascent forms of social discrimination that would seriously undermine core values of our society. Individual decisions taken collectively, if promoted and supported as a matter of public policy, could amount to a new form of eugenics that would threaten a foundational ethical premise of our democratic republic: human beings as such have a high degree of dignity and worth and are owed respect regardless of their specific characteristics.

If the forces that ultimately drive germ-line interventions were left strictly a matter of personal choice, economic ones would prevail (see Chapter 19 in this volume). The promise of huge profits would propel researchers and clinicians to discover and apply germ-line techniques that they could sell to well-to-do individuals and couples. Interventions carried out for enhancement would do better in the market than those geared toward treatment, for there are greater numbers of children unaffected by genetic disease available for enhancement than there are children with disease-related genes for therapy. Allowing the privileged to enhance their gametes but denying the opportunity to those less well-off would put the former at a competitive advantage. This would exacer-

bate the already unjust gulf between rich and poor in our society. Furthermore, it would promote genetic discrimination between those who have been enhanced by means of germ-line interventions and those who have not.

Since research on human embryos is not federally funded, a privately funded industry focused on human germ-line interventions would be likely to emerge. If left to its own devices, it would be shrouded in secrecy to optimize the possibilities of achieving profits from its research in this competitive field and of avoiding ethical and legal scrutiny. Such secrecy would have an adverse effect on the development of germ-line interventions, for it would undermine trust, peer review, and cooperation within the scientific community, making it easier for unproven and unreliable research results to be introduced. A research industry that hoarded genetic information would hamper progress in other areas of genetics and medicine as well.[15]

## Oversight of Germ-Line Interventions

We share a collective responsibility to ensure that germ-line interventions, should they reach the point of application, proceed in an ethically and socially sound manner. It would be foolhardy and dangerous to leave a technology with such significant social implications a matter of private concern. This is not to ignore the importance of the personal experience and choices of individual human beings in procreation or the value and dignity of each human being. Rather it is to argue that we should attempt to ensure that the human community within which we live together is expressive of those values and standards that are essential to its and our survival and well-being, giving individuals as much freedom in personal choice as possible. We cannot fall back on the judgment of a limited number of scientific experts about the uses to which germ-line interventions should be put, no matter how well-intentioned or scientifically creative they might be.

Some degree of oversight of germ-line work is inevitable and necessary. Yet draconian regulations that stifle the development of relevant scientific knowledge and skills are neither desirable nor likely to be effective. Comprehensive guidelines that are sensitive to the demands of scientific investigation, the reproductive aspirations of individuals, and the values and goals of our society need to be established before germ-line interventions begin. Who should be responsible for developing such guidelines?

The Food and Drug Administration (FDA) claims oversight and review au-

thority over any proposed therapeutic modifications to recombinant DNA in gametes or embryos. Yet legally it is charged with investigating the safety and efficacy of experimentation having to do with drugs, biologics, and devices. It does not have standing to engage in open, interdisciplinary discussion of the ethical and social implications of the human research that it regulates, nor does it have a mandate to encourage open national debate on controversial issues.[16] Indeed, quite the reverse is the case. The FDA is required to make final decisions behind closed doors, leaving the public with no direct assurance that the agency has carried out its reviews appropriately and has carefully monitored on-going research involving human subjects.

Until recently, the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH) had the authority to review federally funded research protocols involving recombinant DNA, as well as private-sector protocols sent to it voluntarily. In effect, it operated as a national institutional review board for research into recombinant DNA. It also functioned as a national ethics advisory board to address ethical and policy issues related to research into recombinant DNA. It had the power to ask for public deliberation and input from many constituencies. The role of the RAC as a national review board was ended in 1996, however.[17] It now has only symbolic authority and cannot prevent protocols it considers questionable from proceeding.

In view of the pressing public policy questions raised by germ-line interventions, and the recent revelations of irregularities in gene therapy research that have put patient safety in doubt in the public mind,[18] it is imperative not only to restore the previous authority of the RAC, but to expand it in ways that would allow it to address public policy questions more fully. Moreover, it is advisable to move this body out of the NIH, where it is in an untenable position in that it is responsible to those whom it is supposed to supervise. Possible homes for the RAC would be in the Department of Health and Human Services or, if the new President's Council on Bioethics were assigned a permanent role, were given a clear-cut charge, and were selected by publicly accountable methods,[19] as an arm of that body.

Before the RAC or other authorized body could seriously consider allowing germ-line interventions to proceed in human beings, it would need to:

- determine whether other procedures currently being developed would offer a scientifically, socially, and ethically preferable alternative to germ-line interventions

- receive strongly supported assurances that no deleterious short-term or long-term consequences follow from current experiments with somatic gene transfer
- ascertain that germ-line techniques have been tested thoroughly on other primates and have been shown to be safe, reliable, and reproducible, insofar as this can be determined by risk/benefit assessments
- receive strongly supported assurances that germ-line interventions would be safe in humans and would create no short-term or long-term deleterious physical consequences in the resulting children. These assurances should include that germ-line interventions are at a stage where they replace deleterious genes by homologous recombination, rather than by gene addition. They should also include that a reasonable method of justifying and carrying out a risk/benefit evaluation that extends into the future for several generations has been developed; this could use the two-pronged standard described above: (a) that the risks of germ-line interventions for future persons, insofar as they can be known, should be no greater than their risk of being born with the genetic condition at issue and (b) that no germ-line interventions should be undertaken that *might,* to the best of our knowledge, affect persons who would be born beyond the reach of those known risks
- assess the consequences of failed germ-line experiments in human beings
- receive strongly supported assurances that the reproductive technologies on which germ-line interventions depend create no short-term or long-term deleterious physical or psychosocial consequences in the resulting children or in their descendants for several generations into the future
- carry on public discussions to ascertain the social and moral implications of using germ-line interventions and whether these would be ethically acceptable
- outline a plan for just access to approved uses of germ-line interventions for those without the financial means to obtain them

Only if the results of these inquiries indicate that it would be acceptable to move ahead cautiously with germ-line interventions in human beings, should the RAC or other authorized body then proceed to:

- establish guidelines for the use of germ-line interventions in both the public and private sectors that have some resilience so that they can be adapted to changing situations
- establish a system for monitoring the use of germ-line interventions in both the public and private sectors to ensure that guidelines are being followed
- promote public discussion and education about the scientific, social, and ethical implications of the use of germ-line interventions with the goal of overcoming genetic and related forms of discrimination

While calls to allow personal liberty and scientific initiative to flourish have special resonance within our society, the possibility of introducing germ-line interventions into our genetic armamentarium raises concerns about other values that also are of great significance to our society. Government in a constitutional democracy has a responsibility to engage in anticipatory discussion of such issues and to provide open national review of scientific research and practice proposals related to the alteration of human genes. Moreover, government has the authority to develop reasonable comprehensive guidelines for the use of germ-line interventions in both the public and private sectors to protect the interests of tomorrow's children and the core values of the community.

NOTES

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CHAPTER NINETEEN

# To Market, To Market

## Effects of Commerce on Cross-Generational Genetic Change

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In this chapter we explore the potential effects of commerce on human inheritable genetic modifications (IGM), whereby interventions are made that affect the inheritance patterns of future generations. We are interested in how market forces will influence their development and use. It is our thesis that forces driving the market, including perceived investment opportunities and projected public demand, are more likely than other factors to be determinative. Specifically, we will argue that enhancement applications more than medical uses will determine the scope, direction, pace, and acceptance of IGM research and applications. We also discuss a series of issues that must be carefully assessed if society is to lend its support to a market-driven approach to the development and use of IGM.

### The Forces of Commercialization in Science

As others have observed, we live in the age of "*Homo Economicus,*"[1] in which science is increasingly an object of commerce. In the past decade, we have witnessed on a routine basis newspaper headlines such as "University Research Is

Increasingly Commercial," or "Wall Street Makes It Official: Biotech Has Arrived."[2] What must be considered a fundamental shift in the way science is considered is that the economic value attributed to scientific discovery is no longer just in the products that may be forthcoming. It is also linked to the pure knowledge generated by research. A new paradigm is emerging, one that treats knowledge as a valuable currency in the marketplace. This is clearly reflected in the rush to patent all sorts of newly discovered genetic findings without, in many cases, a clear connection to a useful application.[3] It is also manifested in the efforts of large pharmaceutical companies to invest in academic research in order to obtain exclusive marketing rights to new knowledge that may or may not lead to marketable products.[4] The companies obviously believe the investment is worth the gamble. Knowledge is increasingly becoming the global currency of the twenty-first century.[5]

In the United States, the emergence of this new paradigm can be traced to the early 1980s, when concerns about lagging industrial growth and increased global competition led government officials to urge scientists "to lower the barriers between academic and industrial research."[6] Both Congress and the executive branch supported policies designed to foster closer collaboration between universities and industry. The centerpiece of those policies was the Bayh-Dole Act of 1980 (P.L. 96-517), which gave universities the rights to patentable inventions produced with federal funds. This made the universities attractive partners to industry, providing "powerful economic incentives for the commercial exploitation of science and sent a signal to researchers and their institutions that it was acceptable, indeed encouraged, for them to market their discoveries."[7] The effects of these policies are reflected in data showing U.S. colleges and universities claiming significant royalties from inventions licensed to industry. From 1998 to 1999 alone, royalties for such institutions increased 10 percent, the rate of patent filings by 17 percent, and the number of licenses to industry executed was up by 7 percent.[8]

Not everyone embraced this new entrepreneurial role for academic scientists. Some saw it as a development that began "to alter the ethos of science"[9] in a way that would be inconsistent with the true mission of the universities. Others were more blunt, referring to these new university-industry partnerships as the "prostitution of science to profit."[10] Nevertheless, major research programs now under way would either not exist or would lag far behind in their contribution to useful knowledge without industry support. Examples include stem cell research, somatic gene transfer research, and the Internet. Few would

turn back the clock to the pre–Bayh-Dole Act era, and many acknowledge the benefits to society from such partnerships. Nevertheless, there continue to be concerns that such collaborations foster secrecy over openness; lead to skewed research priorities that favor the potential for profit over more pressing public needs; encourage pursuit of research opportunities more on the basis of available capital than on scientific rigor; and raise the possibility of conflicts of interest among researchers that could affect their judgment in recruiting subjects for experiments, interpreting data, and reporting their findings.[11]

## The Tale of Somatic Gene Transfer Research

The science of somatic gene transfer, which would be the underpinning of eventual treatments for genetic diseases at the molecular level by altering a cell's genetic content, can be viewed as a microcosm of the intersection of science and commerce. It is an especially good example of the situation in biotechnology, where developments "are increasingly linking the biomedical sciences with the aggressive commercialization that is invading nearly every sector of human life."[12] The presence of industrial support for this field of research is pervasive. For example, about one-third of all gene transfer trials on the National Institutes of Health's protocol list have corporate sponsorship.[13] Further, large pharmaceutical companies continue to acquire biotech companies engaged in gene transfer research. All of this industry support has produced a flourishing gene transfer research community in the United States.

Genetic modification approaches came under fire for excessive risk taking following the death of Jesse Gelsinger and others in clinical trials in 1999.[14] Still, the science has been advancing, with two studies reported in early 2000 and one in 2002 that demonstrated improved patient health.[15] By looking at the evolution of this new field we may detect certain features that mirror developments in other scientific fields with heavy industry funding, and it may offer us a window through which to view how increasing commercialization will affect human IGM research and applications.

Concern that industrial funding would skew research priorities in science appears warranted in the case of potential gene therapies. The focus of the field has recently moved away from rare genetic disorders, which initially motivated most research but are now viewed as offering limited profits because of the small numbers involved, to more common ailments, with the promise of greater profits. There are those who believe that there will continue to be move-

ment in the direction of "the most profitable human conditions because there is even far more money to be made in curing baldness and wrinkles than there ever will be in cancer or HIV/AIDS."[16]

The concern about the effects of commerce on science is reflected more broadly in the belief that financial considerations more than scientific rigor may be determining what and how research is conducted and has also surfaced in the context of potential gene-based therapies. As early as 1995, the former director of the National Institutes of Health questioned whether "the intense commercial interest in gene therapy is prompting a stampede into clinical trials and pressure for quick results—before the basic science has been worked out."[17] Two months later in a major story on gene transfer research, *Time* magazine reported allegations that "some doctors have been too hasty, launching clinical trials early in hope of 'cashing out' when a large drug company buys their firm."[18]

The potential for economic gain is very real and problematic for science. There is a concern that financial reward will compromise researchers' judgments about what problems to pursue, the recruitment of research subjects, the interpretation of data, and the openness with which they share information about the research with others, including subjects and their families and institutional and government officials. There is the risk of losing public trust and confidence in science if economic self-interest is seen as substituting for or adversely affecting scientific integrity or the protection of research subjects. This is what may be occurring following the revelations of the recent deaths and other adverse effects associated with gene transfer experiments, and the role that industry involvement may have played.[19]

In the controversy surrounding reports in late 1999 of the deaths of several patients enrolled in gene transfer clinical trials,[20] it was revealed that the lead investigators in three of those experiments had large financial stakes in the outcomes of the research, with two of them having founded competing biotech companies.[21] In addition, it was reported that companies had sought to limit their public disclosure of adverse events to the government during the clinical trials.[22]

While there is no direct evidence that the insufficiencies found by the U.S. Food and Drug Administration in one set of clinical trials[23] or the failure of researchers to report fully and in a timely manner the occurrence of adverse events were influenced by their alliances with biotech companies or by the promise of personal financial gain, these events have put a spotlight on the in-

fluence of commerce on gene transfer research. The perceived economic value of gene therapies, like the commercialization in science more generally, creates an incentive for researchers and companies to keep secret anything that reflects poorly on the progress of their work. The fear that reporting anything negative will frighten away sponsors or deflate stock prices is evident in the statement released by the Biotechnology Industry Organization (BIO) during the height of the controversy over the failure of reporting adverse events. "Virtually every detail about the design, size or status of a clinical trial is of potential competitive value," including details of "adverse events," which, according to BIO, "are, by definition, trade secrets and confidential commercial information."[24]

Clearly, if the public comes to perceive the alliances between leading gene transfer researchers and biotech companies less as a virtue necessary to advance science and more as a vice to preserve personal financial gain or industry's bottom line, then the loss of public trust will put this field of research at risk. The concerns expressed about the influence of commercial support on gene transfer research are equally relevant to IGM research and its uses, perhaps even more so if one takes the position, as we do, that private-sector funding is likely to play an even greater role in the development of IGM applications than it does now in potential gene therapies. We now turn to that part of our analysis.

## Enhancement Trumps Medicine's Traditional Role

As noted earlier, private-sector support for gene transfer research has moved away from rare genetic disorders, which are viewed as having little potential for payback, toward more common ailments that promise greater profits. IGM is also likely to follow the push and pull of the market for at least two reasons. First, as noted in Chapter 7 in this volume, there are few genetic diseases for which such intervention would be compelling. And second, while there will certainly be those for whom preventing the passing on of a lethal disease to the next generation is their primary motivation for using IGM, the main market for such applications will be enhancement of a range of human qualities. For our purposes, enhancement does not refer to alleviating health deficiencies or the risk of disease, but rather to augmenting human characteristics that without intervention would be considered normal.

Indeed, initial private-sector investment in gene therapies may simply be an intermittent step along the way to a broader market. For example, the president of Anticancer, Inc., a San Diego company working on a genetic cure for

baldness, has publicly stated that FDA approval will be sought for marketing the product for hair regrowth in cancer patients who become permanently bald due to chemotherapy, but that once such approval is granted a marketing strategy will be put in place to reach all those experiencing permanent baldness.[25] Gene transfer experiments by academic researchers have demonstrated the possibility of returning color to gray hair by restoring pigmentation in the hairs of albino mice by correcting a gene defect in the hair follicle. This development led a biotech company official to remark that "gene therapy has just taken a cosmetic step forward. . . . Hair follicle research is an area that . . . has enormous commercial potential."[26] If today it is baldness and hair color, then why not improved athleticism or intelligence tomorrow? If gene therapy could be used to prevent loss of muscle strength among elderly persons,[27] then why not use it to enhance one's competitive advantage in athletic competition? If gene therapy can produce a smarter mouse with improved performance on a range of learning and memory tasks that are passed on to offspring,[28] can the attempt to produce more intelligent humans be far behind? Once these technologies are available for legitimate medical applications, absent restrictions that now do not exist, they will inevitably spread to other, more profitable uses.

Obviously, science has a way to go before these possibilities become a reality in humans, if indeed they ever do. Our point is that if developments in IGM are left to the market, private investment will be directed to where the profits are to be made, and that will be in enhancement.[29] Surveys have shown that 40 to 45 percent of Americans approve of using gene therapy to bolster physical and intellectual traits.[30] We suspect that as more people get used to the idea, it will become even more appealing. After all, "we in Western culture are enhancement enthusiasts. . . . Life for us is one long project of self-improvement."[31] Americans already avail themselves of cosmetic surgery to enhance body image, hormones to increase height, and drugs and herbs to promote sexual performance. And we expect and praise parents for doing all that they can to enhance their children's well-being not merely to equip them for a highly competitive environment, but also because it is "the natural expression of parental affection."[32] So it is not surprising when we learn of competition for slots in a highly prized magnet school program that "is fueled by anxious parents who view magnet programs as their children's best hope of future success."[33] For some of these parents and those that follow them, IGM will be seen as a logical extension of what is commonplace throughout America today, with the technology allowing them to achieve their goals more efficiently in many cases.

We already see signs of this happening in the reproductive arena, which may be the best indicator of what lies ahead for IGM technology. Web sites offering donor egg and sperm (as well as surrogate mothers) now exist where couples can enter height, weight, hair color, IQ, profession, and athletic ability in order to find just the right match.[34] And market forces have begun to affect egg donation, where couples, "eager for the best genes money can buy," have engaged in "bidding wars" for certain donors.[35]

## The Case of Assisted Reproduction Technologies

These "markets" for eggs and sperm elicit very emotional responses, thought by some to be their last, best hope for children; by others, nothing more or less than a trade in human tissue. These concerns and many others arise, in subtle and complex ways, in the evaluation of assisted reproductive techniques generally. In addition to the matching of donors with recipients, assisted reproduction clinics (or "IVF clinics" as, initially at least, their main service was in vitro fertilization) deal with general fertility issues. This includes assessing fertility and prescribing treatments as necessary to achieve a live birth. These treatments may include stimulation of egg production by drugs, fertilization of eggs ex utero (sometimes by intracytoplasmic injections of whole sperm), and by extension may include the finding of donors of eggs or sperm, or even surrogate mothers for couples whose problem is the inability to carry a successful fertilization.[36]

The need for assisted reproduction techniques, especially those for women, has grown rapidly, particularly in the past decade. Because these procedures are only beginning to come under scrutiny and potential regulation, the actual number of procedures is difficult to calculate, and the reasons for the apparent increase in procedures have not been completely sorted out. The most obvious reason for the increase is the delay in reproduction that many women have chosen compared to women fifty years ago. There are many different measures of infertility, and many anecdotal stories of increasingly older women bearing children. But by most clinical measures, there is already some loss of fertility by a woman's early to mid-thirties, and by forty, the chance of becoming pregnant any month is approximately 5 percent, compared to 20 percent in any one month for women under thirty.[37] Assisted reproduction clinics are increasing in number and pushing the scientific envelope in developing treatments for female infertility.[38]

Outside of the clinics proper, there are issues bearing more on acquisition than on the procedures themselves. This is manifested in what have become virtual bidding wars for certain types of donors. Advertisements of compensation for egg donors for as much as $100,000,[39] and on-line services offering eggs from models are extreme cases, but in a way not atypical. Although it is illegal to pay for the exchange of human tissue, compensation for time and discomfort is allowable, and those rates are apparently open for negotiation. Egg "brokers" work to assure good matches between donors and recipients, but their fees can be astronomically high, and these costs must be absorbed by the recipient(s) before any procedures have even taken place. Couples or women sometimes ask for specific donors, while donors can advertise themselves. The interaction between donors and recipients can drive up what was once a $1,000 to $3,000 inconvenience-and-discomfort fee to tens of thousands of dollars,[40] and arguments over compensation for what seem to be basic elements of the donation (travel, lodging, food) can become struggles for all parties involved.[41]

The industry is not entirely unregulated. Individual states may have laws that apply. For example, the California Penal Code states that it "shall be unlawful for anyone to knowingly use . . . embryos in assisted reproduction technology, for any purpose other than that indicated by the sperm, ova, or embryo provider's signature on a written consent form." At the federal level, the Centers for Disease Control and Prevention (as a result of Public Law 102-493, 42 U.S.C. 263a-1 et seq., The Fertility Clinic Success Rate and Certification Act of 1992) published a model certification program for embryo laboratories; the requirement for certification could be made law by the states.[42] It is important to note that the certification process would be concerned with a limited number of issues, for the most part with confirmation of success rates and the disposition of "spare" embryos (or, as the technology develops, eggs).[43] If a state chooses not to make the process law, clinics will continue to have the discretion to handle individual procedures (and postprocedure activities) as they see fit.

The Federal Trade Commission has intervened by issuing multiple "cease-and-desist" orders to clinics in an attempt to stop false advertising.[44] The problem may worsen with the expanded reach of the Internet. Already, one informal study of fertility clinic Internet sites concluded that "competition among a large number of clinics for customers has led to heightened and often misleading claims of success rates and promise of techniques that will maximize

the chance of having a child."[45] More recently, the Food and Drug Administration announced in a July 6, 2001, letter to fertility clinics[46] that it has "jurisdiction over human cells . . . involving the transfer of genetic material by means other than the union" of sperm and egg. The letter notes that "the use of . . . genetically manipulated cells (and/or their derivatives) in humans constitutes a clinical investigation and requires submission of an Investigational New Drug (IND) to FDA." The FDA considers such genetic manipulation experimental and plans to apply its authority over clinical studies to some of the treatments used by fertility clinics.

Still, none of the regulation concerns itself with the price of assisted reproduction procedures. Because these procedures are generally not covered by insurance, there are no "reasonable and customary" rates as a basis for comparison and few, if any, clinics advertise their rates. In addition to the costs associated with the treatments, there may also be a cost associated with obtaining sperm and eggs, and as noted in the section above, there have been cases of escalation of "compensation" costs (particularly for eggs) to the point where it could appear to a reasonable person that human tissue is being bought and sold.

The preselection of embryos for specific traits or of sperm for improving the chance of selecting a specific sex are also subject to commercial forces. Although there are good arguments for using preselection to avoid genetic disease, infertility clinics advertise specifically for the purpose of "family balancing,"[47] or sex-selection. There is now at least one confirmed report of preselection carried out for the purpose of providing a specific genetic background for the treatment of a previous-born sibling with a genetic disease.[48] These and other procedures have surfaced in an industry where "there are strong economic interests in expanding services within a highly competitive marketplace. Aggressive marketing of services by 300-plus clinics has been joined by mobilization of various support groups to lobby for expanded investment in these services. In this process, the risks and concerns over the use of the techniques have been all but ignored."[49]

How does this experience with the assisted reproduction community bear on the arguments about the potential for a nonmedical market for IGM? The lessons seem quite clear—there will be some individuals who view germ-line interventions not only as desirable but also as necessary, and, with enough money, will be able to find someone to carry out such procedures.

## The Challenges of Commerce

Earlier we discussed some of the concerns raised about the effects of commercialization on the conduct of gene transfer research and we have concluded that they would be equally relevant to IGM, if not more so because of our speculation that private-sector investment will find enhancement applications offering an attractive market. Beyond research, there are other challenges posed by the market's effect on the availability and use of IGM technology as a method of enhancement that require further consideration.

Although the human body has long been exploited for commercial gain, as reflected in the popular appeal of athletes and models, and in the more recent emergence of surrogate mothers willing to gestate, for a fee, another woman's child, the buying and selling of human body parts evokes deep feelings of uneasiness in our society. Perhaps most troubling to us is the commodification of children suggested by ordering them according to certain specifications. We do that every day with cars; what does it mean if we do that for children? Are we in danger of moving from a relationship built on unconditional love and acceptance to simply trading goods?

The issue of commodification parallels growth of the biotechnology industry, where, over time, the body has come to be valued not merely as a vessel for our personal existence, but increasingly as a resource to be mined for marketable research materials, clinical applications, and consumer products.[50] Discomfort about the increasing commercialization of the human body is reflected in the recent guidelines adopted by the National Institutes of Health (NIH) that would prohibit anyone undergoing fertility treatment from selling embryos in "excess of clinical need" for research purposes.[51] Only donation would be permitted. Nevertheless, market forces are very powerful, and the natural desire of parents to enhance the quality of life of their children will fuel further research and development into IGM that will require society to confront its uneasiness over commodification in the face of these strong commercial forces. Not all social values are well served by the push and pull of commerce.

The pursuit of IGM through predominantly market forces may lead to increased disparities between certain parts of the population. Not everyone can be expected to have access to these technologies where cost is a factor. Although it remains to be seen just how costly these interventions will be, the technologies will still likely be out of reach of many who may desire them; that is the

nature of a marketplace. Increasing the gap between those able to pay and those not may lead to discrimination against those children whose parents were unable to purchase the "right genetic stuff" for their offspring. These matters raise issues of justice that are discussed in Chapter 9 in this volume. For others, however, the fear is not so much that these interventions will be expensive and thus leave many "behind," but rather that they will be inexpensive, leaving those who choose not to use such interventions open to ridicule, or worse.

Another concern stemming from increased reliance on quick fixes spurred by technology and by the market is the possibility of a reduction in effort and resources devoted to understanding and improving underlying social and environmental factors that influence development in concert with genes. There may also be less appreciation for the value of more traditional means—the social interaction in small classrooms or the hard work required to become an elite athlete may create value in itself that a genetic intervention may never achieve.

Finally, a focus on the marketability of genetic enhancement may cause us to overemphasize genetic determinism and lead to less understanding of and appreciation for nongenetic influences that help produce human qualities that we admire. Despite concerns voiced by various professional groups about using genetic modification, especially in the germ line, in an attempt to influence characteristics ranging from athletic prowess and musical ability to personality and intelligence in the absence of adequate understanding of how environmental factors influence human capacities,[52] a growing deterministic view about genes is already slipping into our popular culture.[53] It may be wishful thinking to expect clinics engaged in genetic enhancement to draw public attention to the environmental and human experiences that influence gene expression and help shape who we are.

## Conclusion

The ultimate challenge for public policy that our analysis raises is how much of the future of inheritable genetic modifications is to be ceded to the marketplace. Since the 1932 publication of *Brave New World,* government involvement in procreative decision making has been everyone's worry. It may be, however, that in the twenty-first century, we must look elsewhere for the source of our concerns. It may not be government, but rather a highly individualized marketplace fueled by an entrepreneurial spirit and the free choice of millions of

parents that should prompt society to reflect more deeply on the path that lies ahead.

ACKNOWLEDGMENTS

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CHAPTER TWENTY

# Recommendations for Policy

Mark S. Frankel, Ph.D., and Audrey R. Chapman, Ph.D.

The technologies of inheritable genetic modifications (IGM) will be highly seductive to those who welcome them as a positive step toward shaping our genetic future. Their appeal, however, must be weighed against the uncertainty associated with their safety and the profound ethical and religious questions raised by conscious efforts to design our descendants. As advances in genetics move us ever more closely to a threshold decision on IGM, the AAAS study proposed a number of policy recommendations (see Appendix B), some of which have become even more compelling in the light of events occurring since it was published. This chapter considers those new developments in reviewing both the context and substance of policy recommendations.

## Balancing Scientific Freedom and Responsibility

Inheritable genetic modifications (IGMs) are likely to generate both high hopes and uneasiness. Currently, it is the policy of the federal government not to "entertain proposals for germ line alterations."[1] This is not a policy of pro-

scription; there is no explicit ban on such research. Rather, it is a policy that takes the view that it is premature on scientific and ethical grounds to proceed with IGM. Presumably, if these conditions were to change appreciably, the government would reconsider the policy. Certainly, change will not occur without allowing research to proceed at some level, concurrent with appropriate oversight and a societywide dialogue on the moral questions surrounding IGM. This policy imposes a heavy responsibility on scientists and their institutions, whether academic or commercial. Society expects scientists to pursue research within the constraints of established social controls, such as those to protect the rights and welfare of human subjects, and according to the norms and ethical traditions of the scientific community. To act responsibly, therefore, with respect to IGM means not engaging in such research until public oversight mechanisms are in place to review proposals, while also supporting educational efforts to help scientists and the public consider the broader implications of the research.

Yet, in 2001 researchers reported "the first case of human germline genetic modification resulting in normal healthy children."[2] The research involved the transfer of ooplasm from donor eggs into the eggs of women with recurring failure of embryos to implant in their uteruses. An inadvertent consequence of this procedure, which the clinic reported had "led to the birth of 30 babies worldwide,"[3] was that the donated mitochondrial DNA, as well as that of the birth mother, was found in the cells of those babies born by this method. The report was met with ethical disapproval in some quarters of the United States[4] and British commentators reminded us that the procedure would be illegal in the United Kingdom.[5] In light of the uncertainties regarding the safety of mitochondrial manipulation in the germ line,[6] and the lack of informed discussion of the ethical and social implications of the work, it is imperative that we move quickly to implement a system of oversight that will enable us to make informed and reasoned choices about what place this and other IGM technologies should have in our society. The remainder of this chapter outlines the rationale and thrust of what we believe is the needed system of oversight.

## Effective Public Oversight

There are basically four reasons for instituting a system of public oversight for IGM.

### *Public Safety*

We must be vigilant to protect the safety of those participating in experimental studies, a moral imperative even more critical with IGM research since the well-being of future children will be affected. Concern for public safety is heightened by the intense commercial interest in genetics research and potential applications, where pressures for quick results—and profits—have led to claims that a rush to clinical trials has outstripped our understanding of the basic science involved.[7]

### *Social Values*

While the private sector can contribute valuable resources in developing IGM, the public interest requires the promotion of broad social values, such as freedom of scientific inquiry, assurances that people in need will have access to benefits derived from research, and that decisions on the uses of IGM will be openly vetted in the arena of public discourse. Effective public involvement will help to ensure that the scope and direction of IGM research reflect adequate attention to public priorities.

### *Transparency*

A system of oversight that promotes openness and the sharing of scientific data and findings is more likely to produce better science and expose unacceptable practices than a system biased toward secrecy. For IGM to progress, researchers must have ready access to data and experience from other studies.

### *Public Confidence*

If the public does not trust a system of oversight to protect human subjects or to preserve and promote important social values, then research will not, and should not, go forward. Recent deaths associated with somatic gene experiments and more traditional human subject research have heightened public misgivings about the ability of current oversight mechanisms to offer adequate safeguards for experimental subjects.

## Current Status of Oversight

Experience with somatic gene therapy research raises serious doubts that society is adequately prepared to proceed with IGM research in the absence of

more effective public oversight. An array of bodies now oversee and regulate somatic gene research, including Institutional Review Boards, biosafety committees, the Office for Protection from Research Risks (recently renamed the Office for Human Research Protections) in the Department of Health and Human Services, the Food and Drug Administration (FDA), and the NIH's Recombinant DNA Advisory Committee (RAC). However, recent disclosures of deficiencies with informed consent procedures,[8] the lack of full disclosure of serious adverse outcomes,[9] charges of financial conflicts of interest among researchers in the field,[10] and at least two deaths in clinical trials at prestigious universities have thrown the adequacy of this system of oversight into serious question.

If IGM were to become widely available, consumer access, whether for medical or nonmedical applications, would likely be through clinics such as those that now offer a range of assisted reproductive technologies to couples. These in vitro fertilization (IVF) clinics have prospered during the past decade with increasing consumer demand for access to new technologies that offer infertile couples the hope for a healthy, genetically related baby. And IVF clinics are eager to meet those demands by offering a range of services, including, for example, treatments to allow postmenopausal women to bear children and for couples to achieve "family balancing" via techniques that increase the odds of having a child of a particular sex.[11] The industry is virtually unregulated, however, leaving couples to fend for themselves in a highly competitive environment. This has led to an industry where couples seeking the "best genes money can buy" have precipitated bidding wars over certain donors,[12] where advertising by some clinics has been called questionable, if not deceptive,[13] where the process of informed consent used by some clinics has been described as "seriously deficient,"[14] and where allegations of negligence have led to lawsuits against IVF clinics and practitioners.[15] The AAAS study was concerned about the absence of effective public oversight for this commercial sector and worried that IGM technologies would become another "off-the-shelf" product that the industry will promote to attract customers. In July 2001, the FDA took the position that it has "jurisdiction over human cells . . . involving the transfer of genetic material by means other than the union"[16] of sperm and egg, and that such genetic manipulation is experimental, thereby requiring FDA approval to proceed. That authority has yet to be tested, however, either by the courts or by the resources that will be invested in enforcement. Even if the FDA's jurisdiction in this matter is confirmed, it would not advance the public discussion on

these issues in a manner that we have recommended. The FDA has no mandate to examine the broad ethical, legal, and social issues raised by the procedures or technologies that it regulates.

## Establishing Public Oversight

The incidents involving mitochondrial DNA described earlier make it clear that the science is moving ahead. In the interest of ensuring that society is prepared for these developments, the AAAS report recommended that a system of oversight be in place.

The oversight system would be responsible for:

- promoting a national conversation (and encouraging international participation as well) on the acceptability of IGM for therapeutic and enhancement applications, and under what conditions human research and application could proceed
- designing a mechanism for assessing the risks and benefits, including ethical, religious, and social implications, associated with human IGM, and weighing that assessment against alternative means to achieve similar goals
- encouraging a national effort to develop guidelines to govern the use of IGM
- developing guidelines for managing conflicts of interest among IGM researchers and funders
- serving as a national repository for all data generated by IGM-related research and applications in animals or humans

In view of the work with mitochondrial DNA, we recently recommended that an oversight system "be put in place immediately"[17] and that "no research or clinical applications involving humans should proceed that have the direct or indirect potential to cause inheritable genetic modification in either the public or private sector until [a] body reviews and approves it."[18] We call further for broad public discussion to determine the extent to which there is support for going forward with research that could result in germ-line changes. We offer several "points to consider" by the proposed system of oversight on these matters. It should aim to produce guidance on the following:

- applying the assessment of benefits and risks to the use of IGM in particular cases

- designing a plan to maximize access to relevant data produced by all IGM research and applications, with proper consideration of patient confidentiality and the protection of proprietary data. Public safety and the advancement of knowledge should weigh heavily when determining what data should be made public and the timing of the release
- selecting subjects to participate in IGM research
- developing an appropriate consent process for IGM research
- identifying the parameters of appropriate public-private partnerships
- providing just access to approved uses of IGM for those without the means to obtain them

We believe these steps are justified in order to ensure that such interventions are as effective and safe as possible and consistent with accepted social values.

## Conclusion

The AAAS report concluded that inheritable genetic modifications cannot be carried out safely and responsibly on humans using current methods for somatic gene transfer. Some scientists have moved ahead in the absence of public consensus or oversight, and we believe these actions are premature. Where the genetic endowment of future persons will be affected, public safety must be paramount. Currently, we have little experience and no hard evidence of the long-term safety of IGM on humans. Moreover, we are venturing into territory without any sense of where the boundaries should lie, let alone what it means to cross such boundaries. The prospect of shaping the genetic inheritance of future generations raises major ethical and religious concerns that require sustained and thoughtful deliberation.

One of the challenges posed by IGM stressed in the AAAS report and in the essays in this volume is the need for public education and public discussion to determine whether, and if so, how to proceed with developing IGM for human use. Ideally, these efforts should be informed by an understanding of the relevant science, involve an extended discussion of the cultural, religious, and ethical concerns associated with IGM, and be as open and inclusive as possible. Of critical importance in conducting such a public dialogue will be the design of strategies and structures that are open to all voices that wish to be heard. It is imperative that we understand the possibilities that lie ahead so that we can make informed and reasoned choices about the future.

NOTES

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APPENDIX A

# Consent Form for Participation in a Study of Inheritable Genetic Modification

Julie Gage Palmer, J.D.

## Preface

Our working group originally considered writing a model protocol of an imaginary inheritable germ-line modification (IGM) study, complete with a consent form. We thought we might put this model protocol through its regulatory paces, to teach ourselves and others about the technology and the regulatory system through which an IGM protocol would pass. After some discussion, the model protocol was shelved as premature and inefficient, but the consent form survived as a potentially useful educational tool and as a mechanism for highlighting issues that might not otherwise be noticed.

In reading this consent form, one should keep in mind that the consent process involves much more than obtaining a research subject's signature on a form. Other materials, such as videotapes or descriptive written materials, are often included in the consent process. After receiving the consent form and learning about the proposed study, subjects should always have time to consult other experts, clergy, and legal counsel, and to ask detailed questions of the researchers before signing the form.

This consent form is based on a fictitious scenario. The technology necessary to perform the described experiment does not currently exist. Therefore, there are bracketed sections of the form that are left ambiguous. At some future time, it may become possible to fill in these sections with greater detail. Or, perhaps the whole scenario will require change. A first IGM experiment might not involve two homozygotes with the same genetic disease. It is impossible to predict where the science will take us.

## Consent Form

### *Purpose*

We, _____ and _____, are husband and wife. Both of us are homozygous for Gaucher disease type II and/or type III. We understand that Gaucher disease arises from a deficiency of an enzyme, glucocerebrosidase, which is responsible for changing glucosylceremide to glucose and ceremide. We understand that we are being invited to participate in a medical research study. The study is being conducted by [names of institution, group, and/or individual investigators], (collectively, the "investigators"). The study protocol has been approved by the Institutional Review Board of [name of institution]. The purpose of the study is to determine the safety and efficacy of replacing the faulty glucocerebrosidase gene that causes Gaucher disease with the normal (or "wild type") gene in [eggs and sperm before fertilization or in fertilized eggs, known as "zygotes," or in early developing embryos before implantation, known as "preembryos."]

Currently, the standard treatments for Gaucher disease involve expensive enzyme infusion every two weeks in children and adults who have the disease or, when patients have an HLA-matched sibling, risky allogeneic bone marrow transplants. We have each received one or both of these treatments and understand the procedures, benefits, and burdens involved.

We understand that the ultimate goal of this study is to develop new methods for preventing or treating disease. One day these techniques may allow researchers and doctors to prevent or treat genetic disease before conception or implantation, by using recombinant DNA methods to correct the errors in DNA that give rise to disease. Because IGM is experimental, however, we understand that the study investigators cannot guarantee any particular results.

We understand that IGM involves the manipulation of eggs, sperm, and/or preembryos in vitro (that is, in a dish in the laboratory) and therefore requires the use of in vitro fertilization (i.e., fertilization in culture fluid in the laboratory, known as IVF). After gene replacement, preembryos will be relocated to the wife's uterus through embryo transfer (ET) procedures. Neither IVF nor ET is considered an experimental procedure, but IGM is considered experimental.

The investigators strongly recommend that participants in this research study who become pregnant undergo either chorionic villus sampling (CVS) or amniocentesis, which are standard techniques for prenatal diagnosis of genetic disease and chromosomal abnormality. CVS or amniocentesis will be im-

portant to determine whether the gene transfer was successful and to confirm that gene transfer has not interfered with embryo or fetal development. If prenatal diagnosis demonstrates that gene transfer has been unsuccessful or that the developing fetus has an abnormality caused by the study procedures, we may face a difficult decision about pregnancy termination. If we refuse prenatal diagnosis against the investigators' recommendation, we assume the risk that we may deliver a child with genetic or developmental disabilities.

*Description of Research Procedures*

We understand that this research study will proceed in stages. Many, and frequently all, of the procedures can be accomplished through outpatient visits. Generally, the stages are:

1. inducing and monitoring development of eggs in the wife's ovaries
2. collecting eggs from the ovaries
3. collecting sperm from the husband
4. putting these eggs and sperm together in the laboratory, enabling possible fertilization and growth of preembryos to occur
5. gene transfer of the normal gene into the zygote, sperm, or eggs
6. early embryo growth
[7. analyzing the genes of unfertilized eggs and/or of preembryos after gene transfer, but before embryo transfer]
8. transferring the preembryos into the uterus
9. prenatal diagnosis by CVS or amniocentesis

A more detailed description of these steps follows.

1. *Inducing and monitoring development of eggs in the ovaries*

To control the timing of egg maturation and to increase the chance of collecting more than one egg, fertility drugs (Clomid and/or Pergonal and/or Lupron and HCG) are selected and administered to the wife. On the beginning of her menstrual cycle (and sometime before the onset of menstruation), she will receive one or more injections daily for a period of up to twenty-eight days. The drugs and doses may vary between study participants, depending on medical and related factors. These fertility drugs stimulate the ovaries to develop fertilizable eggs.

Ultrasound examinations will be performed on the wife daily after a period of two weeks to check on the development of the stimulated ovarian follicle(s)

in which the egg(s) are ripening. Blood specimens will be collected from the wife to assist in predicting the time of expected ovulation and in scheduling egg recovery. Blood specimens will be taken by inserting a needle in a vein on a daily basis for up to fourteen days.

2. *Collecting eggs from the ovaries*

Eggs will be collected from the ovaries by a method known as "ultrasound-guided transvaginal oocyte (egg) retrieval," which involves guiding a hollow needle connected to a suction device into the ripe follicles for aspiration of the eggs contained within them. An ultrasound machine image is used as a guide for positioning the needle tip. The wife will be placed on an examination table and, with ultrasound guidance, the needle will be inserted through the vagina into the peritoneal cavity and into the follicles contained within the ovary. As many as thirty eggs may be collected from the follicles. Generally, between eight and ten eggs are retrieved.

Local anesthesia, with or without some intravenous sedation, is generally required for successful egg retrieval by this method. Ultrasound-guided transvaginal oocyte retrieval is performed on an outpatient basis. Usually, patients may leave the office within one to two hours following the procedure.

3. *Collecting sperm from the husband*

The husband will, in proximity to the laboratory, provide a fresh semen specimen by masturbation on the day of his wife's egg retrieval. The sample will be processed in the investigators' laboratories to prepare the sperm for fertilization. The husband's sperm will be used to fertilize eggs that have been obtained from the wife's ovaries. We understand that we must abstain from sexual intercourse three to five days before the retrieval to ensure a good-quality semen specimen.

4. *Fertilization in the laboratory*

The eggs and sperm will be placed together in a special culture fluid and kept in incubators in the investigators' laboratories for approximately twelve to eighteen hours to allow fertilization to occur.

5. *Gene transfer*

If fertilization occurs, [insert specific procedures for gene transfer].

Gene transfer will be attempted on all of the zygotes obtained through IVF.

The procedures described above in section 5 are the experimental components of this research study.

6. *Early preembryo growth*

After gene transfer, appropriate laboratory conditions will be used to encourage cell division, which may or may not occur. If division does not occur within twenty-four hours in any of the treated zygotes or zygotes arising from treated sperm and eggs, that zygote will be discarded.

7. *Analyzing the genes of unfertilized eggs and/or of preembryos*

Just before fertilization, an oocyte (egg) undergoes a cell division, producing a small cell known as a "polar body" plus an ovum that is ready for fertilization. After the ovum is fertilized, it undergoes several cell divisions before the cells differentiate. The undifferentiated cells of a four- to eight-cell preembryo are known as "blastomeres." The cells of a five- or six-day-old preembryo have differentiated to some extent, and the outermost layer of cells (which are destined to become the placenta) is known as the "trophoderm." A biopsy to obtain a cell or cells for genetic analysis will be performed at one of the following three developmental stages: (1) before fertilization, the polar body may be removed and analyzed; (2) after fertilization, a blastomere may be biopsied and analyzed; or (3) cells may be removed from the trophoderm of a five- or six-day-old preembryo.

The biopsied cells will be subjected to chromosomal, biochemical, and/or DNA analysis. If genetic analysis takes longer than preembryos can be safely maintained in the laboratory culture fluid, the preembryos will be stored by cryopreservation (freezing) for [number of days].

After analysis, investigators will transfer to the wife for gestation those preembryos they believe are free from the faulty glucocerebrosidase gene that causes Gaucher disease. [Insert whether heterozygous preembryos will be transferred.] Preembryos that are not transferred because they are thought to have [one or] two copies of the faulty gene will be [allowed to degenerate]. (Any preembryos that have been cryopreserved will be thawed before transfer.)

[The cell biopsy and preimplantation genetic diagnosis described here are currently experimental.]

8. *Transferring the preembryos into the wife's uterus*

At a time determined by the investigators, the preembryo(s) will be transferred into the uterus through a small tube inserted through the vagina and

cervix into the uterine cavity. The investigators will transfer as many preembryos into the wife as can be obtained by using IVF and the gene transfer procedures, up to and including [four] preembryos [unless the husband and wife give written instructions that fewer than four preembryos shall be transferred].

Transferring more than one preembryo could result in the growth of more than one fetus. According to medical literature, if two to four preembryos are transferred, the risk of multiple pregnancies resulting is approximately 20 percent, two-thirds of which are twins. There are cases in which transfer of four preembryos may result in triplets or, on rare occasions, in quadruplets. Twin pregnancies could cause increased risk of prematurity, hypertension, and many other complications for the fetuses and mother. Higher order multiple pregnancies always deliver prematurely, approximately four to six weeks early for triplets and six to eight weeks early for quadruplets. Such severely premature infants are at risk for many complications, including death.

Although ET may involve some discomfort, anesthesia is usually not required. A few hours of bed rest generally follows the preembryo transfer. Intramuscular injections or suppositories of the hormone progesterone may be given after ET to aid in implantation and growth of the preembryo(s).

Several blood samples may be taken from the wife during the few weeks after ET to determine her hormone levels and to decide if pregnancy has occurred and is proceeding normally. Ultrasound examinations may also be required.

If more than four preembryos are obtained through IVF and gene transfer and if we have consented to long-term storage by cryopreservation, the excess preembryos will be frozen and stored by cryopreservation. A separate consent form for cryopreservation must be signed if this option is chosen. Cryopreserved preembryos may be thawed and transferred to the wife in later natural cycles if another attempt at pregnancy is desired. If we have not agreed to cryopreservation, the excess preembryos may be allowed to degenerate, donated to other couples, or donated to research as directed by us on a separate form.

9. *CVS or amniocentesis*

If a pregnancy is achieved, either CVS during the first trimester or amniocentesis during the second trimester is strongly recommended to verify whether the fetus(es) that has/have developed from the transferred preembryo(s) is/are developing normally and that gene transfer has been successful.

We will be asked to sign a separate consent form at that time. If an affected fetus is found by CVS or amniocentesis, the possible outcomes and options will be discussed with us.

*Risks*

We understand that there are risks associated with the procedures for achieving IVF/ET and gene transfer and with any pregnancy resulting from these procedures, including the risks described below and any other risks that have been disclosed to us. We freely assume the risks associated with IVF/ET and with gene transfer. We understand that the investigators will not be liable for any occurrence for which we have assumed the risk.

The fertility drugs administered to the wife may cause side effects. The side effects that may result from administration of these fertility drugs include nausea, hot flashes, headaches, and/or visual halos. The use of Clomid or Pergonal may result in complications, including ovarian cyst formation, swelling, pain, fluid collection in the abdomen and lungs, bleeding into the abdomen, shock, and/or blood clots. An allergic reaction to any of the drugs is also possible. The use of ovulation-inducing drugs in repeated cycles may increase a woman's risk of developing ovarian cancer.

Blood drawing and injections of medications may cause mild discomfort, bruising, bleeding, infection, and/or scarring at the needle sites.

Ultrasound-guided transvaginal oocyte retrieval may cause infection, bleeding, and/or damage to the intestines or other internal organs from the needle. Patients may also experience pain or discomfort during the retrieval process.

Cryopreservation of preembryos may result in destruction of preembryos or unforeseeable harm to offspring. However, research data suggest that embryos that survive cryopreservation and thawing are not likely to be damaged.

ET involves a risk of infection and/or bleeding. A pregnancy following ET may end in a spontaneous abortion (miscarriage), ectopic pregnancy, or stillbirth. Multiple pregnancies may occur with the associated complications described above, including hypertension and premature delivery. All of the risks associated with a naturally occurring pregnancy, including the risks of obstetrical complications, are present for a pregnancy following IVF/ET and gene transfer. Some of these risks may be greater for pregnancy following IVF/ET and gene transfer than for a naturally occurring pregnancy.

The process of IVF/ET can be psychologically stressful. Significant anxiety

and disappointment may occur. Additional anxiety may be produced by our participation in this IGM study. Substantial time commitments by both the wife and husband will be necessary for participation in this study.

Many complex and sometimes unknown factors limit pregnancy rates following IVF/ET. Experimental IGM procedures may further limit pregnancy rates in this study. Known factors that may prevent the completion of an IVF cycle or the establishment of a pregnancy in this study include the following:

1. Follicles containing mature eggs may not develop in the monitored cycle. In such a situation, the attempt at oocyte retrieval will be canceled.
2. Pelvic scarring and/or technical problems may prevent recovery of one or more eggs from the ovaries.
3. There may be failure to recover an egg because ovulation has occurred before the time of retrieval.
4. One or more eggs may not be recovered on attempted aspiration of the follicle.
5. Egg retrieval may produce damaged eggs.
6. Fertilization of the eggs to form preembryos may not occur.
7. The eggs, sperm, or preembryos may be damaged during gene transfer.
8. Cell division of the preembryos may not occur after gene transfer.
9. The preembryos may fail to develop normally. If the investigators, using their best judgment, determine that one or more preembryo(s) are not viable, these preembryos will not be transferred and will be allowed to degenerate in the laboratory.
10. After ET, implantation may not occur.
11. If implantation occurs, the embryos may not grow or develop normally.
12. Equipment failure, infection, human error, and/or other unforeseen factors may result in loss of or damage to eggs, semen sample, and/or preembryos.

Birth defects, genetic abnormalities, mental disabilities, and/or other possible anomalies may occur in children born following IVF/ET and gene transfer just as they may occur in children born following a naturally occurring pregnancy. At present, there is inadequate information to provide an accurate estimate of the risks of these occurrences in connection with this research; such risks may be greater than those associated with natural conception.

The risks from gene transfer include destruction of the eggs, sperm, zygotes, or preembryos, or possible failure of the gene transfer that could result in the offspring having Gaucher disease or some other genetic abnormality induced by the gene transfer. In addition, there may be risks of injury to us, such as the risk of infertility, or damage to our offspring from gene transfer. There may be risks to us or to our offspring associated with the vector used to accomplish the gene transfer, including the risk of cancer or other disease. We understand that IGM as described in this protocol has never before been tested in human beings and that there may be other, mild, moderate, or severe risks to ourselves, our offspring, or our descendants that are currently unknown and unforeseeable.

*Benefits*

A benefit of this research may be that couples who seek IGM in the future might avoid genetic diseases in their children, grandchildren, and future generations. Possible benefits of this research to us include the avoidance of Gaucher disease in our child(ren).

We understand, however, that this is a research study. Neither becoming pregnant nor the avoidance of Gaucher disease in any fetus or child can be assured. No guarantee has been made to us regarding the outcome of these procedures.

*Alternatives*

The reasonable alternatives to IGM in connection with IVF/ET as a method for avoiding or treating Gaucher disease in our child(ren) have been explained to us, along with their risks, benefits, and potential outcomes. Depending on our particular circumstances, these alternatives include some or all of the following procedures:

1. IVF/ET and preimplantation genetic diagnosis (a research procedure) and selection of embryos [Note: this alternative does not apply to the scenario of a homozygous couple.]
2. Natural conception followed by prenatal diagnosis (using amniocentesis or CVS) and termination of pregnancies involving affected fetuses [Note: this alternative does not apply to the scenario of a homozygous couple.]
3. Natural conception with the associated risk of giving birth to an affected child who could be treated with traditional medical therapies

for Gaucher disease (or with a future innovative treatment, not yet discovered)

4. Adoption of a child or children
5. ET or zygote intrafallopian transfer (ZIFT) with donated preembryos
6. Artificial insemination of the wife using donor semen
7. Surrogate mother arrangements
8. IVF/ET or gamete intrafallopian transfer (GIFT) or IVF/ZIFT using donated eggs

*Confidentiality*

We understand that information obtained about us during this study will be treated as confidential and that our identity will not be revealed intentionally without our prior consent, except in the following circumstances. In their review of this research study, the Food and Drug Administration and/or the National Institutes of Health may have access to all information concerning our participation in this study. In addition, we understand that any medical records related to this study may be inspected by the Institutional Review Board of [name of institution]. Representatives of collaborating institutions, suppliers of the vectors used in this study, and other similar institutions may have access to our records. We also agree that specific medical details about us may be included in medical or other publications as long as reasonable efforts are made to conceal our identity.

It is possible that our participation in this research study may aid in the development of techniques that help other couples and/or that new and useful medical information may be obtained. Accurate and appropriate information may be made available to the public with respect to public concerns that may arise from the study. We consent to the taking and publication of photographs and to audiovisual taping of laboratory procedures, provided our identity is not disclosed without our permission. In addition, we consent to the observation of procedures or laboratory work by researchers, students, medical personnel, or medical reporters who are guests of the investigators, provided our identity is not disclosed without our permission.

*Research-Related Injury*

In the event the wife is injured as a direct result of our participation in this study, gynecologic treatment by [insert name of institution] will be provided to her free of charge. Such free treatment will [will not] include other medical

specialists' care, nursing, hospital care, or medications. We will be responsible for those costs as well as the costs of pregnancy, complications of pregnancy, medical, hospital, or nursing care for our fetus(es) and offspring, and any other medical care for ourselves. [Obviously, this is an example that will change depending on what is offered by an institution.]

In the event of research-related injury to one of us or to our offspring, we understand that monetary compensation for any such injury or for associated costs will [or will not] be available from [insert name of institution].

*Contact Persons*

If we have any questions about this research, or in the event of research-related injury, we may contact [insert name and telephone number]. If we have any questions about our rights as research subjects, we may contact [insert name and telephone number], who is chair of the Institutional Review Board.

*Voluntary Participation*

Our participation in this research study is voluntary. We understand that we may refuse to participate or withdraw our consent for this research at any time without penalty, prejudice, or loss of benefits to which we would otherwise be entitled. If we withdraw from the study after it has begun, we may be asked to cooperate in undergoing laboratory tests and/or examinations.

We understand that early withdrawal from the study may result in the following adverse medical consequences: withdrawal after ovulation has been induced, but before eggs have been harvested, could result in a multiple pregnancy of affected children, miscarriage, pain, and/or severe risks to the mother and fetus(es). [Insert other risks of early withdrawal.]

*Termination of Participation*

If the investigators feel that it is appropriate to withdraw us from the study for any reason, they will do so. If we are withdrawn from the study by the investigators, we may be asked to cooperate in undergoing laboratory tests or examinations.

*Long-term Follow-up*

We understand that evaluation of the long-term safety and efficacy of gene transfer requires long-term follow-up. We are expected to cooperate in long-term follow-up that extends beyond the active phase of this study. We agree to

cooperate with this long-term follow-up whether or not we complete the entire active phase of the study. Even if we withdraw from the study or are withdrawn by the investigators, we agree to cooperate with long-term follow-up.

During the follow-up period, we should address any questions we may have to [insert name and telephone number].

We understand that any significant findings resulting from the study will be made known to us in a timely manner, including new information about the experimental procedures, the harms and benefits experienced by other individuals involved in the study, and any long-term effects that have been observed.

*Request for Autopsy*

To obtain vital information about the safety and efficacy of gene transfer, permission will be requested for the autopsy of the mother, father, and our offspring at the time of their deaths, no matter what the cause. We should advise our families of this request and of its scientific and medical importance.

*Additional Costs*

We acknowledge that we have been made aware of the costs associated with this study, and we agree to be responsible for them. We understand that insurance coverage for all or any part of these procedures may not be available. We understand that we will not be responsible for the costs of gene transfer [insert any other free procedures], but that we will be responsible for costs including hospital charges, laboratory charges, physicians' professional fees, medication, and travel and lodging expenses [insert any other items of additional cost]. We understand that we are also financially responsible for any additional medical costs incurred by us as a result of complications and for other medical care that might be required as a result of participating in this study, except as specifically outlined above in the Research-Related Injury section of this form. We acknowledge, jointly and severally, our personal responsibility for payment of all of these associated costs. In the event that we withdraw from this research study or are withdrawn by the study investigators, we will be responsible for any financial costs incurred by us before our withdrawal.

*Additional Considerations*

We acknowledge that any child born to us through IVF/ET and gene transfer is our own legitimate child and our heir with all of the rights and privileges accompanying such status.

We consent to the degeneration of zygotes or preembryos that, in the best judgment of the investigators, are not viable. We consent to the disposal or use for research of other cells, body tissues, or fluids that may be obtained during the research procedures.

[If investigators intend to protect technology, either products or procedures, arising out of this study under patent or trade secret laws, insert a paragraph here about these proprietary rights and what steps will be taken to permit as full communication as possible among investigators, clinicians, and research subjects concerning research methods and results.]

We understand that the interpretation and effect of this consent form shall be governed by the laws of the State of [insert].

*Agreement to Participate*

We have carefully read and considered the contents of this consent form. We have had an opportunity to ask questions about this research study. All of our questions have been answered to our satisfaction. We understand the procedures, risks, potential outcomes, alternatives, and other matters described in this document and otherwise described to us by study personnel. [If study subjects have seen a slide presentation, videotape presentation, or other written materials, these should be referenced here.]

By affixing our signatures, we voluntarily consent and agree to participate as research subjects in the described research study. We accept and assume the associated risks. We acknowledge that there is no certainty that we will achieve a pregnancy or live birth of a child free of genetic disease, and that no guarantee has been made to us regarding the outcome of these procedures. Neither inducements nor promises have been offered by [insert name of institution] or any of its physicians or representatives.

We have received a copy of this consent form _____ [number of days or weeks] in advance of signing it. We have had adequate time to reach our decision and have reached our informed decision voluntarily.

_____ _____

(signature of wife) (date)

_____ _____

(signature of husband) (date)

_____ _____

(signature of witness) (date)

*Physician's Certification*

I certify that I and/or my representatives have consulted with the above-named wife and husband, have explained the study to them, and have answered their questions. I believe they fully understand the explanations they have received as well as the answers to their questions.

_____ _____

(signature of physician) (date)

_____ _____

(signature of witness) (date)

*Representations*

We will notify the study investigators in writing of any change in our current address and telephone number, which are listed below.

_____ _____

(address) (telephone)

_____ _____

(signature of wife) (date)

_____ _____

(signature of husband) (date)

_____ _____

(signature of witness) (date)

# AAAS Report on IGM

## Major Findings, Concerns, and Recommendations

A majority of the project's working group members endorses the following findings, concerns, and recommendations.

### Findings

- The working group concluded that IGM cannot presently be carried out safely and responsibly on humans. Current methods for somatic gene transfer are inefficient and unreliable because they involve addition of DNA to cells rather than correcting or replacing a mutated gene with a normal one. They are inappropriate for human germ-line therapy because they cannot be shown to be safe and effective. A requirement for IGM, therefore, is the development of reliable gene correction or replacement techniques.
- With current gene addition technologies, iatrogenic genetic damage could occur as a result of the unintended germ-line side effects of somatic cell therapy. These problems seem at least as great as the harmful genetic damage that might arise from intentional germ-line transfers. Therefore, attention must also be given to the accompanying side effects of somatic cell therapies already in use or planned.
- The working group identified few scenarios where there was no alternative to IGM for couples to minimize the prospect that their offspring will have a specific genetic disorder. The further development of somatic cell gene transfer, moreover, will offer more options for treating one's offspring.
- Guided by the theologians—mainline Protestant, Catholic, and Jewish traditions—and ethicists on the working group, the group concluded that religious and ethical evaluations of IGM will depend on the nature of the technology, its impact on human nature, the level of safety and efficacy, and whether IGM is used for therapeutic or en-

hancement purposes. Ethical considerations related to the social effects of IGM, particularly its implications for social justice, will play a major role in shaping the attitudes of religious communities.

- To date, the private sector has played a prominent role in the funding of somatic cell genetic research, raising questions about the influence of commercial interests on the conduct of researchers and on the scope and direction of the research. Similar questions are likely to surface if IGM research and applications go forward.

## Concerns

- The ability of IGM to shape the genetic inheritance of future generations raises major ethical concerns. IGM might change attitudes toward the human person, the nature of human reproduction, and parent-child relationships. IGM could exacerbate prejudice against persons with disabilities. The introduction of IGM in a society with differential access to health care would pose significant justice issues and could introduce new, or magnify existing, inequalities.
- IGM for enhancement purposes is particularly problematic. Enhancement applications designed to produce improvements in human form or function could widen the gap between the "haves" and the "have-nots" to an unprecedented extent. Efforts to improve the inherited genome of persons might commodify human reproduction and foster attempts to have "perfect" children by "correcting" their genomes. Some types of enhancement applications might lead to the imposition of harmful conceptions of normality. The dilemma is that IGM techniques developed for therapeutic purposes are likely to be suitable for enhancement applications as well. Thus, going forward with IGM to treat disease or disability will make it difficult to avoid use of such interventions for enhancement purposes even when this use is considered ethically unacceptable.

## Recommendations

- Even in advance of a decision about whether to proceed with IGM as traditionally understood as gene transfer in reproductive cells, a public body should be assigned responsibility to monitor and oversee re-

search and developments in IGM, more broadly conceptualized as any technique aimed at modifying the genes that a person can transmit to his or her offspring. Some interventions that fall within the scope of the working group's definition of IGM are already taking place without the oversight that we believe is necessary.

- It is important to promote extensive public education and discussion to ascertain societal attitudes about proceeding with IGM and to develop a meaningful process for making decisions about the future of this technology. These efforts should be informed by an understanding of the relevant science, involve an extended discussion of the cultural, religious, and ethical concerns associated with IGM, and be as open and inclusive as possible. International consultation on these matters should also be encouraged.
- If a societal decision is made to proceed with IGM, a comprehensive oversight mechanism should be put in place with authority to regulate IGM applications in both the public and private sectors. Such a mechanism would help to promote public safety, develop guidelines for the use of IGM, ensure adequate public participation in policy decisions regarding IGM, and address concerns about commercial influence and conflicts of interest.
- Any protocol for somatic cell transfer in which inheritable modifications are reasonably foreseeable should not proceed without assessing the short- and long-term risks and without proper public oversight.
- Before IGM can proceed, there should be a means in place for assessing the short- and long-term risks and benefits of such interventions. Society must decide how much evidence of safety, efficacy, and moral acceptance will be required before allowing human clinical trials or IGM applications.
- At this time, the investment of public funds in support of the clinical development of technologies for IGM is not warranted. However, basic research should proceed in molecular and cellular biology and in animals that is relevant to the feasibility and effects of germ-line modification.
- Human trials of inheritable genetic changes should not be initiated until techniques are developed that meet agreed-on standards for safety and efficacy. In the case of the addition of foreign genetic material, the precise molecular change or the changes in the altered genome should be proven with molecular certainty, probably at the

sequence level, to ascertain that no other changes have occurred. Furthermore, the functional effects of the designed alteration should be characterized over multiple generations to preclude slowly developing genetic damage and the emergence of an iatrogenic genetic defect. In the case in which attempts at IGM involve precise correction of the mutant sequence and no addition of foreign material, human trials should not begin before it can be proven at the full genome sequence that only the intended genetic change, limited to only the intended site, has occurred. If it is shown at the full genome sequence level that the sequence of a functionally normal genome has been restored, there will likely be no need for multigeneration evaluation.

- The role of market forces in shaping the future of IGM research and applications should be carefully assessed to ensure that adequate attention is paid to public priorities and sensibilities.
- Existing conflict of interest guidelines governing research should be reviewed and, where appropriate, amended and vigorously enforced to address the increasing role of commercial interests in genetics research. The guidelines should specify when a financial interest in a commercial IGM venture is grounds for precluding an investigator's direct participation in a clinical trial supported by that company. They should require that investigators disclose any financial interests in the research during the informed consent process, and should prohibit researchers with a direct financial interest in a study's outcome from participating in that study's selection of patients, the informed consent process, or the direction of the study.

APPENDIX C

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